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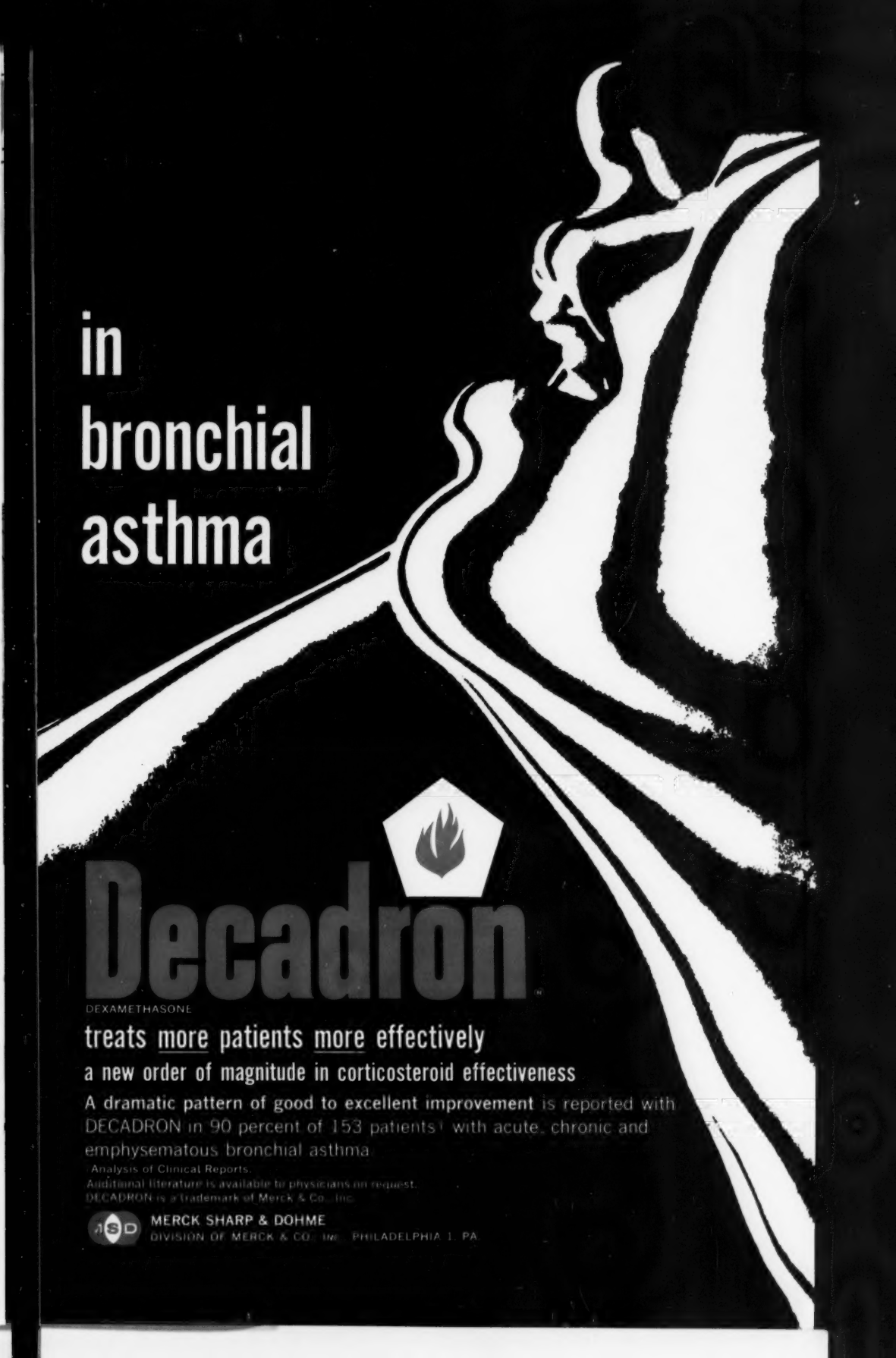
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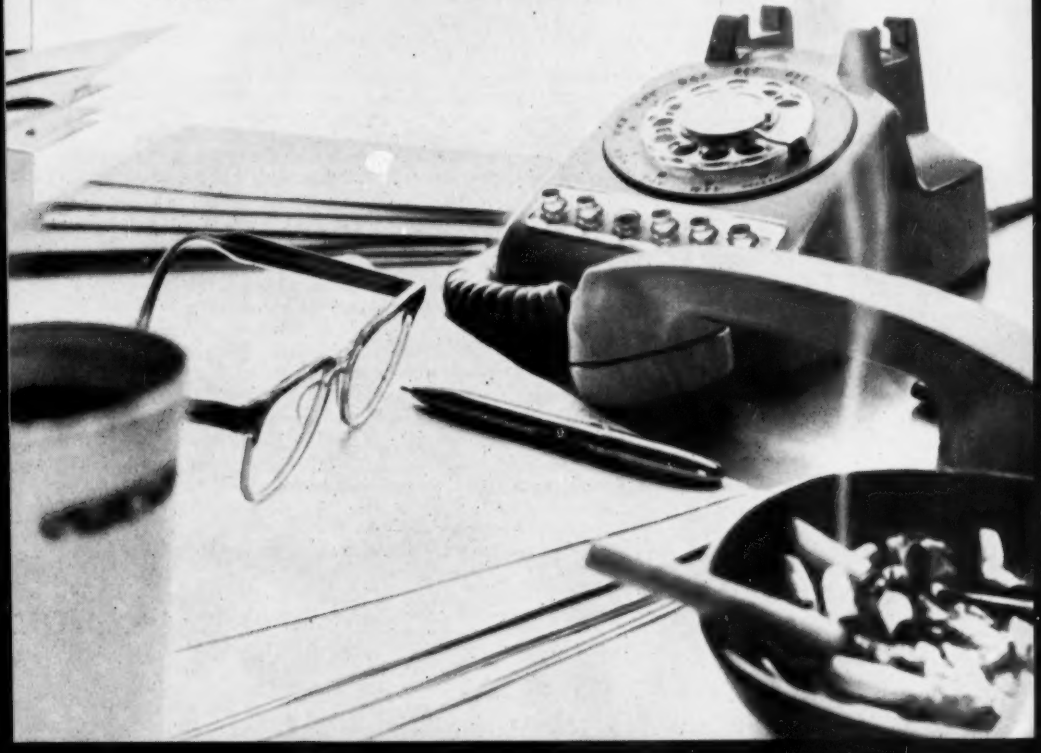

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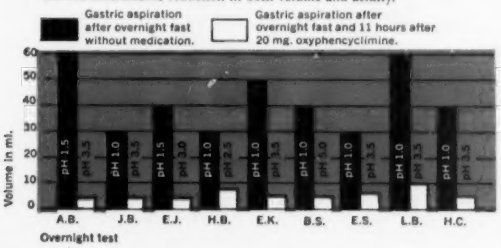

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Editorial

The Art of Consultation

From time immemorial doctors have sought each other's advice about their patients. Hogarth's side-splitting print "A Consultation of Physicians" was published in 1736. By the midnineteenth century the technique and manners of doctors' "getting together" were clearly formulated. Everyone who reads Anthony Trollope will remember in "Barchester Towers," when the old Bishop lay dying, the careful protocol which was followed in having Sir Omicron Pie come down from London to see him. No less entertaining are the passages in "Dr. Thorne" between Dr. Thorne and Dr. Fillgrave, when violation of the niceties of consultation led to the enraged exit of the latter. At any rate, it should be made clear that a consultation is not a haphazard affair but serious business, with "manners" no less rigid than those laid down by Mrs. Post for other fields of human relations.

The first rule of consultation is, of course, that the physicians concerned should actually be present at the bedside of the sick patient. In England, whence stems our own medical protocol, the technical term actually is "to meet." The consultant called by the attending physician says, "I will be glad to meet you" at such and such a time and place. At the meeting, which should be punctual, the attending doctor is, of course, host and should behave accordingly. It is his duty, even if bored, to appear pleased to have the consultant join him. He should introduce him not in glum fashion but in such a way as to impress the patient, if the visit is to be worth while. "Mr. Jones, here is Dr. Topflight. As you know, he's a great specialist in the sort of trouble you have, and we're fortunate to be able to have his advice." It is then the family doctor's job to remain at the bedside during the consultant's examination, ready to answer questions, to give necessary information and, indeed, to participate in certain phases of the proceedings. The examination completed, the attending physician and consultant withdraw and talk over the problem, and, when agreement has been reached about what to do, they return to the patient to convey to him the results of their deliberations. Just as the attending doctor must play the polite host, so it is the duty of the consultant not to belittle the attending doctor or in any way to imply superiority on his, the consultant's, part. One must never give the impression of being in a hurry.

Now this protocol for consultation is not just a stuffy routine; it has developed because only in this fashion can good results be attained. Unfortunately the manners of consultation have been largely forgotten, if ever known, by many

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doctors. It happens only too often that the consultant is simply "turned loose" on the patient, while the doctor ignores his presence, looks out of the window, talks to the nurse or family in a loud voice, and completely detaches himself from the proceedings. Under such circumstances communication breaks down and the consultant, of course, cannot do a good job; it is the patient who suffers.

Nurses are often as much at fault as doctors in violating the etiquette of consultation. As soon as the consultant appears they sometimes seem to go out of their way to impede proceedings by deciding that the patient must at that moment have nourishment or a thermometer or some trivial procedure which could well wait. Frequently the nurse insists on taking the family doctor aside to discourse in a loud voice about the chart or other matters. What she should do is to stand by quietly so as to be able to answer questions or help handle the patient.

Even worse than bad manners at the actual consultation is the current practice of asking a consultant to "drop in" and see the patient by himself. One commonly hears in hospital corridors Dr. A calling to Dr. B as he rushes by, "Oh, 'B,' my patient in 615 seems to have an irregular heart today; drop in and see him for me, will you?" The results of this sort of thing are often chaotic. And yet one step lower is the procedure current in hospitals of writing a note in the chart such as, "Surgical Service! Please see the patient. He has bled from the bowel for three days." All this reminds us of the British stationmaster in a small town in India, who locked himself in the office and telegraphed down the line to his superior, "Large Bengal tiger loose on platform; please arrange."

Another form of consultation, recently much in vogue, is that of presenting the patient to a group, or conference, of specialists. The tumor board, the chest conference, the gastrointestinal conference are examples. A formal "presentation" is usually made by the house officer; the radiologist then shows films; there may be a rudimentary examination of the patient by one or several of the group, after which he is dismissed, and after a more or less formal discussion an opinion as to diagnosis or procedure is rendered, often by majority vote of those assembled. Is this good or bad? Now it is certainly good to give the patient a chance to be seen by a group of supreme specialists, but at times this exercise becomes rather academic. The intimate contact, which is so necessary in evaluating a sick patient as a whole, may be lost, and, like Macaulay's general who preferred to lose battles by the classical rules of tactics rather than to win them by ingenuity, one often feels that sounder results may be obtained if the doctor calls in one or two carefully selected consultants who will deal with the problem as that of a patient and not of a case.

One could go on much longer, but the essence of the matter is obvious. The object of consultation is to clarify a situation; unless the doctors get together with the patient and follow the dictates of ordinary politeness, confusion is bound to occur.

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A Clinical Evaluation of the Iodopyracet (Diodrast) Renogram

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Several different techniques are available for estimating renal function in man. Some of these measure very accurately discrete and specific functions, such as glomerular filtration rate, renal blood flow, and maximum rates at which the tubules can transport materials (Tm). These methods, however, are time-consuming, expensive, and unsuitable for routine clinical use. The clinical methods for estimating renal function, such as the blood urea nitrogen content, the urea or creatinine clearance, phenolsulfonphthalein excretion, and urinary concentrating ability, are reasonably accurate and very useful in evaluating bilateral renal disease. However, these tests rarely are of diagnostic value and, in the absence of ureteral catheterization, are of no value in detecting unilateral renal disease.

Recently, Winter, Taplin, and co-workers[1,2] have introduced a new method for studying renal function, the radioactive iodopyracet (Diodrast) renogram, that appears to be of practical clinical value although it is not a precise measure of any specific function. The radioactive iodopyracet renogram is performed by intravenous injection of a small amount of iodopyracet labeled with I^{131} and measurement of the rate of appearance and disappearance of radioactivity in the renal areas with externally placed scintillation counters. This test, which is simple and safe to perform, offers the opportunity to detect qualitative differences in the function of individual kidneys in certain renal and urinary tract diseases.

The present report is a summary of our experience with 297 bilateral iodopyracet renograms in 222 patients. These include 33 control subjects without known renal or urinary tract disease and 189 patients with a variety of renal or urinary tract disorders, 65 of whom were hypertensive. Clinical situations in which the renogram seems valuable are illustrated. An analysis of the renogram findings in the 65 hypertensive patients is presented briefly. Finally, the results of a comparison of the renogram with the intravenous pyelogram and several clinical tests of renal function as aids in detecting renal impairment are described.

Materials and Methods

The technique of Winter[1] was employed by us, with minor modifications. The patient sits in a chair constructed in such a way that the degree of vertical inclination can be regulated by an adjustable arm and head rest. An x-ray to show the location of the kidneys is essential for proper positioning of the scintillation counters,* which are placed above each kidney and directed along the long axis of the organ. The scintillation counters, mounted on freely adjustable arms,† are connected through rate meters ‡ to rectilinear galvanometric recorders.§ Although no collimators

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* Versatile Scintillation Counter, Model DS5; Nuclear Instrument and Chemical Corporation, Chicago.

† Stand and holder; Nuclear Instrument and Chemical Corporation, Chicago.

‡ Analytical Count Rate Meter, Model 1620; Nuclear Instrument and Chemical Corporation, Chicago.

§ Rectilinear Galvanometric Recorder; Houston Technical Laboratories, Houston, Texas.

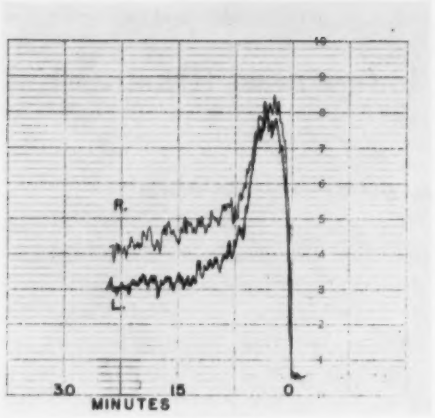


Figure 1

Fig. 1.—Normal radioactive iodopyracet renogram. In this and in the subsequent figures the numbers on the ordinates represent counts per minute × 300. On the abscissa the time is expressed in minutes. Each division is seven and one-half minutes.

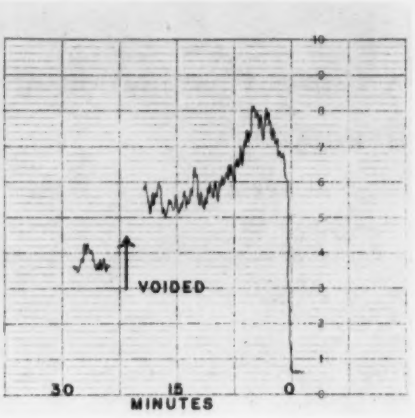


Figure 2

Fig. 2.—Contribution of the bladder urine to the equilibrium phase of a normal renogram.

are used, the lead shields in which the counters are mounted permit sufficient directional collimation. After the patient is positioned, iodopyracet labeled with I^{131} is injected intravenously; 1μc. per 5 kg. of body weight, representing but a few micrograms of iodopyracet, is adequate. The amount of radioactivity in the renal areas is then recorded for 15 to 30 minutes. No special preparation of the patient is required. The test can be repeated within three to four hours if necessary. Four distinct phases may be seen in the normal renogram (Fig. 1). The rapid initial upswing reflects the blood supply to the kidneys and adjacent tissues. During the next three to five minutes a gradual further increase in renal radioactivity is noted. This has been called the "secretory phase" in earlier papers on the renogram. The "accumulation phase" would appear to be a more satisfactory designation, since tubular secretion also undoubtedly occurs during the subsequent clearance or excretory phase, which is characterized by a gradual disappearance of radioactivity over the next 10 to 15 minutes. The latter two phases probably reflect concentration of the iodopyracet by the renal tubules, followed by its excretion into the urinary collecting system. Finally, a stage of equilibrium is reached which represents residual activity not only from the kidneys but also from elsewhere, including the bladder urine (Fig. 2).

Two factors in the interpretation of renograms deserve comment. The right renogram tracing generally is higher than the left in all phases because of the proximity of the liver, which accumulates small amounts of diodrast. Thus, careful positioning and interpretation of the right renogram must be exercised. Recently, Block, Hine, and Burrows[8] have reported that the intravenous injection of small amounts of unlabeled iodopyracet prior to administration of the labeled material blocks the hepatic uptake of the latter. We have confirmed this observation in a few instances.

Secondly, factors such as the position of the scintillation counters, the volume of distribution of diodrast, and thickness of the body wall may affect the height of the vascular spike. This makes quantitative comparisons of the height of the vascular spike from patient to patient most difficult.

Attempts to subject the renogram to quantitative objective analysis have been unsuccessful. Trials to find a measurement or a ratio of vascular, accumulation, and/or excretory phases which could be used as an exact criterion of normal failed. Thus, the general size and appearance of the tracing, with particular emphasis on the inter-relations of the several phases, have been used for evaluating renograms in the present paper. This has resulted in a reluctance to brand minor variations from the typical normal renogram as definitely abnormal. Whenever unilateral abnormalities in the renogram were suspected, repeat studies have been performed in an effort to rule out errors of positioning and errors introduced by the proximity of the liver.

Thus far the only complications encountered in the performance of the 297 renograms have been episodes of transient hypotension and mild syncope in two patients. Both patients recovered promptly when allowed to lie down. In these two instances, the renograms showed a pattern of continuous ac-

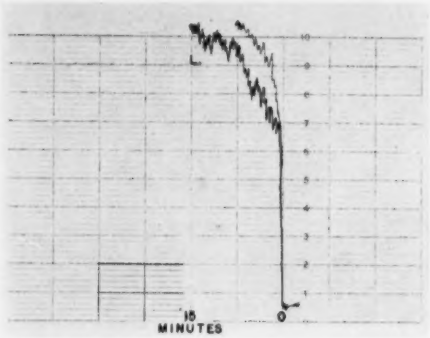


Fig. 3.—Radioactive iodopyracet renogram in a case of neurogenic shock. The rapid and continuous accumulation and the absence of the clearance phase make this tracing similar to that found in cases of acute obstruction. Five days later a repeat renogram did not demonstrate this accumulation.

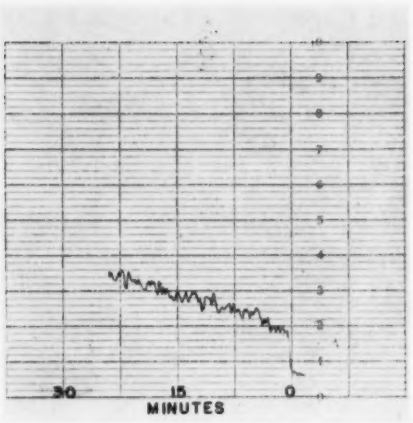


Fig. 4.—Renogram in a patient with partial ureteropelvic obstruction. Note the continuous accumulation of radioactivity.

cumulation (Fig. 3), similar to that described by Winter [1] in neurogenic shock.

Clinical Applications

A. The Renogram in Obstructive Uropathy.—Winter and his colleagues [1,2] have described several different abnormalities which may be noted in the renogram. When renal function is impaired, the height of the vascular spike of the renogram is often markedly reduced, the accumulation phase is reduced, and the clearance phase is delayed or absent. Perhaps the most specific renogram abnormality is that observed in urinary tract obstruction or hydronephrosis. In this situation, a continuous increase in radioactivity following the initial vascular spike of the renogram is characteristic (Fig. 4).

The renogram has been useful in the evaluation and management of patients with obstructive uropathy. It allows close observation of the progress of an obstructive or potentially obstructive lesion; it may serve as an indicator of the comparative reversibility of the disease in each kidney in the presence of bilateral obstructive lesions and may be an aid in the evaluation of lesions responsible for the nonvisualization of a kidney or intravenous pyelography. The following cases are presented to illustrate the types of situations in which the renogram has served useful and sometimes unique purposes.

CASE 1.—A 57-year-old white woman underwent complete abdominal hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic lymphadenectomy for adenocarcinoma of the endometrium. The urine and an intravenous pyelogram obtained a few days before the operation were normal. The blood urea nitrogen was 13.2 mg. per 100 ml. Ten days postoperatively the patient developed gross hematuria, urinary frequency, fever, and right flank pain. An intravenous pyelogram at this time revealed bilateral hydroureteronephrosis. The site of obstruction appeared to be at the level of the inferior margin of the sacroiliac joint. Films made up to seven hours showed continued retention of the contrast medium. The urine contained 4+ protein, many erythrocytes, 40-50 leukocytes per high-power field, and many bacteria. Urine culture revealed Escherichia coli, for which methenamine mandelate was administered. An indwelling catheter did not influence the hydronephrosis, which was thought to be due to ureteral obstruction by a pelvic inflammatory mass palpable by rectal examination. A renogram (Fig. 5*A*) performed at this time revealed evidence of bilateral incomplete obstruction (prolonged accumulation phases and reduced and delayed clearance phases). A renogram obtained two weeks later (one month postoperatively) showed improvement on the left but a more striking hydronephrotic pattern on the right, with complete absence of clearance phase for 35 minutes (Fig. 5*B*). A third renogram taken six weeks after surgery still showed the presence of hydronephrosis on the right. The left tracing was markedly improved (Fig. 5*C*). A retrograde pyelogram

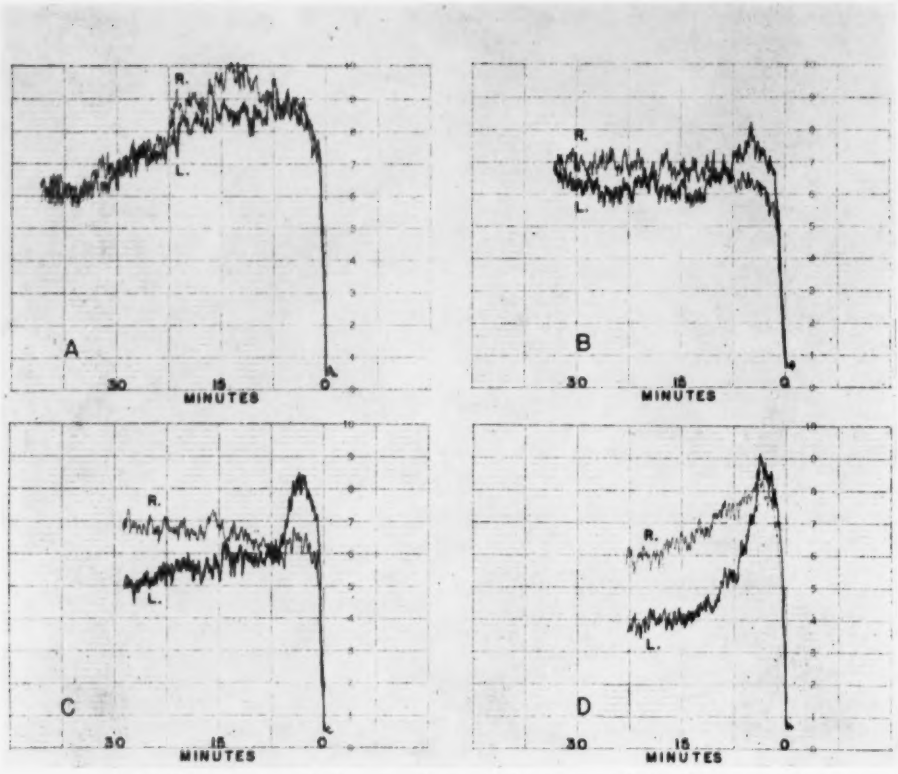


Fig. 5.—Serial renograms in Case 1. *A*, two weeks postoperatively. *B*, one month postoperatively. The right tracing crosses the left at seven and one-half minutes. *C*, six weeks after surgery. Again the right tracing crosses the left. *D*, two and one-half months postoperatively.

at this time revealed persistent moderate hydronephrosis on the right. A ureteral catheter was placed in the right ureter for 48 hours. Subsequent observation at two and one-half and five months postoperatively revealed gradual return of the right renogram toward normal. The left renogram was now normal (Fig. 5*D*). The opportunity to evaluate the renal status at frequent intervals by a simple, safe, and inexpensive test permitted conservative management in this patient.

Case 2.—A 45-year-old white man experienced severe right renal colic. A ureteral calculus causing slight obstruction was demonstrated in an intravenous pyelogram performed just after the attack of colic. Active intervention was postponed, since the patient became asymptomatic and was free of infection. During the next four months the patient had three episodes of ureteral colic. X-rays of the abdomen revealed gradual descent of the calculus. Serial diodrast renograms served to demonstrate the absence of significant obstruction and allowed continued observation without concern for the functional status of the right kidney. The patient passed the calculus four months after the first attack of colic.

Case 3.—A 50-year-old white woman with chronic bilateral renal calculi was hospitalized because of nausea, vomiting, and pain in the left lumbar region. Physical examination revealed a severely ill patient. Blood urea nitrogen was 49 mg. per 100 ml. The urine contained 2+ protein and 40-50 leukocytes per high-power field. Aerobacter aerogenes was obtained on urine culture. A plain film of the abdomen showed stag-horn calculi in both kidneys. An intravenous pyelogram failed to visualize either kidney even after four hours. A retrograde study was attempted, but the ureteral catheter could not be passed beyond the obstructions. These data did not permit a rational basis for the decision as to which kidney should be operated on. Renograms were then performed (Fig. 6*A*). The right renogram was char-

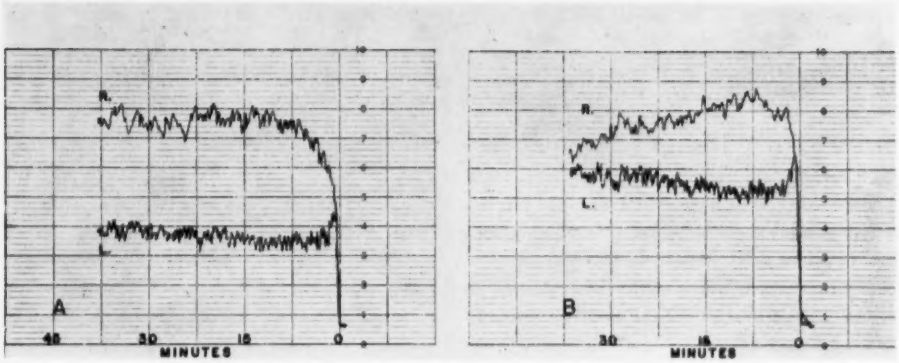


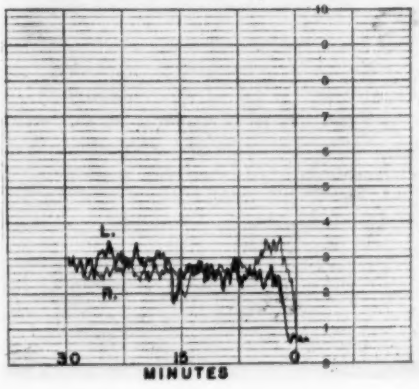
Fig. 6.—Pre- and postoperative renograms in Case 3.

acteristic of severe obstruction with evidence of some residual renal function, as suggested by a good blood supply and by the accumulation of radioactivity. In contrast, the left renogram showed almost no function, with a reduced vascular spike, a short concentration phase, and a poor clearance phase. Since the right renogram revealed evidence of function despite the obstruction to urinary flow, the right kidney was explored. Nephrotomy was performed, with removal of the calculi. Grade II hydronephrosis and an abscess in the upper pole of the right kidney were noted at operation. Despite a rather stormy postoperative course, the blood urea nitrogen decreased from 49 to 27 mg. per 100 ml. the day after the operation and remained at approximately this level thereafter. The urea clearance increased from a preoperative value of 14% to 31% of normal within one week. A renogram obtained 11 days after surgery (Fig. 6*B*) revealed considerable improvement on the right, with a definite clearance phase which, however, was still abnormally prolonged. The left renogram remained unchanged, with practically no evidence of function. Two months after the original surgery an exploration of the left kidney was performed. The kidney appeared large and hydronephrotic. The lower pole was resected, and multiple calculi were removed. A postoperative (23 days) renogram revealed continued absence of function on the left. In this instance, therefore, the renogram provided the only preoperative evidence of the functional status of the two kidneys and led to the selection of the only salvageable kidney for the initial operative attack.

CASE 4.—A 46-year-old Negro woman gave a history of repeated chills, fever, and left flank pain over a period of several years. Repeated intravenous pyelograms showed a normal right kidney but no evidence of kidney function on the left. The urine had a specific gravity of 1.022, no protein, and 25-30 leukocytes per high-power field. Urine culture resulted in a meager growth of Pseudomonas aeruginosa. The iodopyracet renogram revealed a normal right tracing, but the left tracing showed progressive accumulation of radioactivity, suggesting left hydronephrosis in association with severely impaired renal function (Fig. 7). At cystoscopy great difficulty was encountered in finding the left ureteral orifice. The knowledge that the left renogram showed evidence of renal function was responsible for a persistent search. Eventually, a very inconspicuous orifice of the left ureter was discovered. A retrograde pyelogram made at this time revealed left hydronephrosis. The kidney was explored surgically and appeared to contain so little functioning tissue that nephrectomy was performed. The patient has remained asymptomatic since that time.

B. The Renogram in Hypertension.—Winter [1,4] has suggested that the renogram might prove helpful in screening patients

Fig. 7.—Renogram in Case 4. The right and left tracings cross.



with hypertension for unilateral renal disease. With this suggestion in mind, we performed renograms on 65 patients with hypertension. This was not an unselected group of patients, in that a number were studied because of other evidence of renal disease and incidentally also had hypertension. These data, then, do not reflect the true incidence of renogram abnormalities in the general hypertensive population.

Bilateral renograms were normal in 20 of 35 patients with essential hypertension. Bilateral abnormalities of the renogram were noted in the remaining 15 patients with essential hypertension, all of whom had abnormal renal function by other clinical tests, presumably the result of vascular nephrosclerosis. Hypertension was present in 13 patients with diffuse bilateral renal disease, such as chronic glomerulonephritis, chronic pyelonephritis, polycystic disease, or diabetic glomerulosclerosis. Bilaterally abnormal renograms were noted in these 13 patients. In this group other clinical tests of renal function were abnormal.

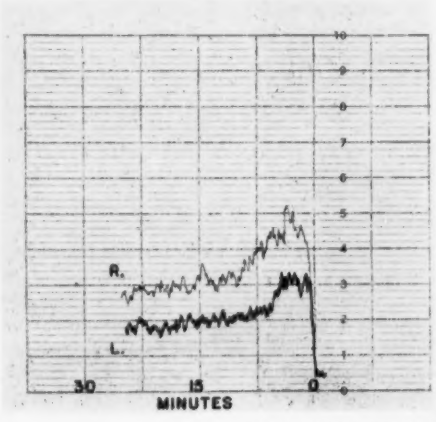
Unilateral renogram abnormalities were observed in 17 of the 65 hypertensive patients. Intravenous pyelograms confirmed the evidence of unilateral disease in nine of these patients but were normal in four. However, aortography demonstrated unilateral renal vascular abnormality in one of the latter patients. Pyelograms were not obtained in the remaining four patients. Collateral information established the cause of the unilateral renal disease in 10 of the 17 patients with hypertension and unilateral renogram abnormalities. Renal calculi, hydronephrosis, or chronic pyelonephritis were present alone or in combination in six patients, while narrowing of the renal artery, renal infarct, renal adenocarcinoma, and congenital malformation were demonstrated in one patient each. The hypertension in all these patients was not necessarily due to the unilateral renal disease. No specific etiology for the unilateral renogram abnormality was established in the remaining seven patients with hypertension, two of whom had reduced over-all renal function as measured by other clinical tests. Perhaps essential hypertension in some of these patients was complicated by more advanced nephrosclerosis in one kidney than in its mate.

We believe that the renogram is a safe, simple, and economical screening device for unilateral renal disease in hypertensive patients. If the renogram should reveal a unilateral abnormality, further diagnostic work should be undertaken. The renogram in itself is rarely sufficient to establish the nature of a unilateral renal disease.

Two case reports illustrating the usefulness of renograms in the evaluation of the hypertensive patient follow.

CASE 5.—Hypertension was discovered on routine examination in a 30-year-old white man. At first the hypertension was quite labile but became sustained when he reached the age of 40. Shortly thereafter the patient developed electrocardiographic abnormalities and infrequent attacks of angina pectoris. At the age of 45, the hypertension became severer, with systolic pressures as high as 230 mm. Hg. The heart size, fundi, and renal function remained normal, but an x-ray of the abdomen revealed a calcium plaque near the origin of the left renal artery. An intravenous pyelogram disclosed no evidence of anatomical or functional abnormality of either kidney, but an aortogram showed narrowing of the left renal artery. The left renogram was distinctly abnormal (Fig. 8). A second renogram confirmed the findings of the first. It was felt that the lesion of the renal artery in this patient developed after the onset of essential hypertension. A trial on

Fig. 8.—Renogram in Case 5.



medical management was instituted prior to serious consideration of surgical intervention, since it was by no means certain that the renal artery lesion was responsible for the apparent increase in the severity of the hypertension.

CASE 6.—A 58-year-old white woman was hospitalized two and one-half years ago for severe hypertension. An intravenous pyelogram showed a normally functioning right kidney and a small nonfunctioning left kidney. An attempt to perform aortography was unsuccessful. A diagnosis of hypertension of renal origin was made. Nephrectomy was advised, but the patient refused. However, further progress of the hypertension (B. P., 250/140 mm. Hg) and the development of hypertensive retinopathy and encephalopathy led to rehospitalization. A renogram revealed a completely normal right tracing. The left tracing showed a low vascular spike and no accumulation or clearance phases (Fig. 9), findings compatible

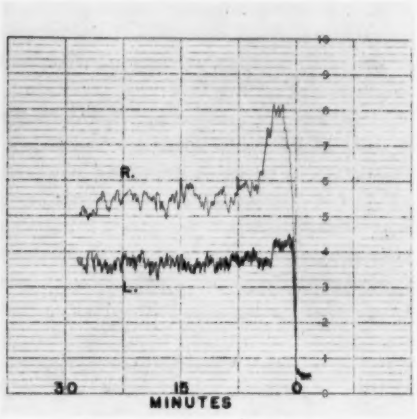


Fig. 9.—Renogram in Case 6.

with a diagnosis of vascular thrombosis and severe impairment of function. The left kidney was removed and on examination was grossly atrophic. Microscopic study revealed chronic and acute pyelonephritis and a recent small infarct. The blood pressure decreased sharply after nephrectomy and has generally remained within normal limits, with only sporadic increases to 170/90.

Renograms and Intravenous Pyelograms Compared as Indicators of Renal Abnormalities.—Renograms and intravenous pyelograms were performed in 100 subjects, 46 of whom had a variety of renal diseases. The remaining 54 patients, 21 of whom had hypertension, had no clinically apparent renal disease. An intravenous pyelogram

TABLE 1.—*Renograms and Intravenous Pyelogram*

	Intravenous Pyelogram		Total Patients
	Normal	Abnormal	
Normal renograms	38	2	40
Abnormal renograms	30	30	60
Total patients	68	32	100

was recorded as abnormal when it revealed a definite anatomical abnormality or when the excretion of the contrast medium was obviously impaired. The sensitivity of the two techniques in detecting renal abnormalities are compared in Table 1, without regard to the type of abnormality present. The renogram detected abnormalities in 30 of 68 patients with normal intravenous pyelograms. Conversely, the pyelogram detected renal abnormalities in only 2 of 40 patients with normal renograms. The renogram was definitely abnormal in 10 of the 54 patients with no clinical evidence of renal disease. Therefore, we believe that the renogram at present is the more sensitive screening test for renal abnormalities.

Renograms and Several Tests of Renal Function (Including Proteinuria) Compared as Indicators of Renal Dysfunction.

Since proteinuria is one of the most sensitive indicators of renal disease, it was not surprising to find normal renograms in 6 of 34 patients with proteinuria (Table 2). Bilateral renogram abnormalities were present in 12 of 53 patients without proteinuria. When proteinuria was moderate to severe (2+ to 4+), abnormalities of the renogram

TABLE 2.—*Renograms and Proteinuria*

	Urinary Protein				
	Neg.	Trace-1+	2+	3+-4+	Total Patients
Both renograms normal	31	6	0	0	37
One renogram abnormal	10	4	1	0	15
Both renograms abnormal	12	16	4	3	35
Total patients	53	26	5	3	87

TABLE 3.—*Renograms and the Blood Urea Nitrogen Level*

	Blood Urea Nitrogen, Mg/100 Ml.			
	8-15	16-20	21+	Total Patients
Both renograms normal	19	17 *	1	37
One renogram abnormal	7	9	4	20
Both renograms abnormal	3	9	27	39
Total patients	29	35	32	96

* Four of these patients had slight abnormalities of doubtful significance in one renogram.

were the rule. The urine contained no protein in 10 of the 15 patients with unilateral renogram abnormalities.

In 96 patients a blood urea nitrogen measurement was available within one week of the iodopyracet renogram (Table 3). A borderline increase in the blood urea nitrogen (16 to 20 mg. per 100 ml.) was not unusual in the presence of normal renograms. However, if the blood urea nitrogen exceeded 20 mg. per 100 ml. the incidence of bilateral renogram abnormalities was high (27 of 32 patients). Similar results were observed in regard to the urea clearance in the 28 subjects in whom this test was performed within two weeks of obtaining the renogram (Table 4). Normal renograms were not infrequent when the urea clearance was moderately reduced. However, marked impairment of urea clearance was always associated with bilateral renogram abnormalities.

TABLE 4.—*Renograms and Urea Clearance*

	Urea Clearance, % of Normal			
Renograms	70+	40-69	10-39	Total Patients
Both normal	6	3	0	9
One abnormal	2	3	0	5
Both abnormal	2	5	7	14
Total patients	10	11	7	28

A similar relationship was observed between the renogram and P. S. P.-excretion test in 41 subjects (Table 5).

TABLE 5.—*Renograms and Phenolsulfonphthalein Excretion*

	P. S. P. Excretion, % in 15 Min.			
Renograms	25+	15-24	2-14	Total Patients
Both normal	11	1	0	12
One abnormal	1	3	4	8
Both abnormal	1	9	11	21
Total patients	13	13	15	41

Summary and Conclusions

The radioactive iodopyracet (Diodrast) renogram is a safe and simple procedure which we have found to be useful in the clinical evaluation of a number of renal and urinary tract diseases, especially those characterized by obstruction.

Bilateral renograms are useful in detecting unilateral renal disease and can be used for this purpose in screening patients with hypertension.

Renograms are a more sensitive indicator of renal abnormality than are intravenous pyelograms. The latter, however, obviously can furnish information not available in renograms.

Renograms can yield qualitative evidence of renal functional impairment but generally are not as sensitive for this purpose as are the usual tests of renal function.

Dr. L. W. Riba referred Case 3 and gave permission to report his clinical findings; Dr. A. R. Colwell Jr., Case 5, and Drs. V. J. O'Connor, J. B. Hurd, and J. K. Sokol, Case 6.

Northwestern University Medical School, Ward Memorial Building, 303 E. Chicago Ave. (11) (Dr. Earle).

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Cholangiolitic Hepatitis

Clinical-Pathologic Studies and Response to Steroid Therapy in Four Cases

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Introduction

A chronic form of hepatitis, which was predominantly obstructive, was originally recognized by Eppinger.[1] Watson and Hoffbauer[2] later used the term "cholangiolitic hepatitis" in referring to patients with a similar clinical picture. In addition, other reports,[3-6] substantiated by epidemiological data, have indicated that acute viral hepatitis is capable of inducing an illness with clinical and laboratory features typical of regurgitation jaundice. In cholangiolitic hepatitis the clinical manifestation of a relative sense of well-being is in marked contrast to the biochemical abnormalities. There are usually an appreciable degree of pruritus (associated with acholic stools), low urinary urobilinogen, hyperbilirubinemia (high direct fraction), bilirubinuria, high alkaline phosphatase, and hypercholesteremia. This is in marked contrast to the relatively normal "flocculation" tests. A review of the previously described cases disclosed many with mildly abnormal hepatocellular tests, and the diagnosis of cholangiolitic hepatitis was used to indicate these predominant clinical and biochemical features of prolonged obstruction. These findings have also been seen in toxic reactions following the use of arsphenamine, methimazole, thiouracil, aminosalicylic acid, sulfadiazine, aurothioglucose, dinitrophenol, cinchophen, manganese salts, methyltestosterone, and chlorpromazine. Hence, patients who present this picture should be questioned carefully for a history of exposure to these chemical agents as well as to the commoner modes of transmission of viral hepatitis. Histologically the liver has been characterized as having a paucity of cellular changes. Variable periportal inflammatory-cell infiltration and bile thrombi localized in the central portion of the lobule have been noted.[1,2,7] It is often difficult to differentiate the clinical and biochemical abnormalities of this entity from extrahepatic obstruction. Experience has shown that liver needle biopsy may not clarify this dilemma, and it has been necessary to resort to cholangiography and direct liver biopsy by peritoneoscope or a small laparotomy incision under local anesthesia.

The use of steroids in the therapy of viral hepatitis has been reported by a number of investigators.[3,8-15] All have noted dramatic improvement in well-being and appetite, accompanied by a prompt fall in the total bilirubin. This latter effect was more dramatic and sustained, with less incidence of relapse, if moderately high doses of steroids were given over a prolonged period of time.[12] However flocculation tests did not indicate significant improvement in hepatocellular function, nor was there a consistent decrease in the inflammatory reaction, as shown by liver biopsy. Even more disturbing was the incidence of relapse. Sborov et al.[12,13] reported 2 relapses in 49 patients, a rate of about 5%. In other smaller series relapse rates have been reported, ranging from 25% to 40%.[3,9-11] This is in sharp contrast to the less than 1% re-

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lapse rate reported by Evans et al.[3] in 3,000 patients with hepatitis who received conventional therapy. A comparable relapse rate has been noted in this hospital in a smaller group of patients; furthermore, anorexia and malaise subsided within one week and complete recovery occurred in six to eight weeks in the vast majority of our patients. Thus, the hepatitis seen here was a relatively benign self-limited disease. Even if it is acknowledged that steroid therapy might permit the average patient with hepatitis to return to normal life one to two weeks earlier, the prohibitive relapse rate as well as the untoward side-effects and complications encountered seem to weigh against their use in typical patients with hepatitis.

The use of steroids in the severer and/or more chronic forms of viral hepatitis has not been uniformly effective.[13] A rapid fall in bilirubin and a prompt relief of symptoms have been noted, but there was often no apparent shortening of the necessary period of hospitalization. A high relapse rate was noted here as well. However, Sborov et al.[12] were impressed with the usefulness of steroids in six cases of cholangiolitic viral hepatitis. Lipschutz and Capson [16] have suggested it might be effective; Johnson and Doenges,[17] in a recent review of this form of hepatitis, reported two cases in which steroid therapy was beneficial.

In view of the usually prolonged course, with recovery not infrequently occurring only after several months, the use of steroids in the treatment of this entity seemed to warrant further investigation. It also seemed pertinent to determine whether the prompt fall in bilirubin could be used as a diagnostic tool in differentiating this clinical entity from extrahepatic obstruction, thereby avoiding the necessity of potentially hazardous surgical procedures. From Jan. 1, 1953, through June 30, 1956, a total of 722 male patients with infectious hepatitis was treated at this hospital (average age, 21.4 years). There were several patients, among the 722 with hepatitis, who had evidence of severe but less protracted functional obstruction, with early associated cephalin-flocculation and thymol-turbidity abnormalities. They have been diagnosed merely as viral hepatitis with an attending functional intrahepatic obstruction. The diagnosis of cholangiolitic hepatitis was applied only when there were protracted obstructive features with essentially normal hepatocellular liver-function tests. Based on the clinical course and serial liver-function studies, the following four soldiers were the only cases in which the diagnosis of cholangiolitic hepatitis was justified.

Report of Cases

CASE 1.—This 25-year-old white man was admitted to a station hospital on Oct. 22, 1954, and transferred to the Second General Hospital 68 days later. Five days prior to admission he noted anorexia and dull right upper quadrant pain associated with mild diarrhea, light stools, dark urine, and, on the day prior to admission, an icteric tinge of the sclerae. There was no known exposure to hepatotoxins.

Significant findings on examination were mild scleral icterus and a firm tender liver, which extended 4 cm. below the right costal margin. Routine laboratory studies were normal. Serial liver-function studies are shown in Table 1. Weekly total protein, A/G ratio, and prothrombin times were consistently normal. There was moderate anorexia, mild pruritus, and progressive weight loss of 30 lb. over the next three months. The liver size remained unchanged. A 24-hour urine urobilinogen on the 70th hospital day was only 1.2 mg., and the 24-hour urobilinogen was 13 Ehrlich units per 100 gm. of feces, demonstrating the prominent obstructive features. A diagnosis of probable cholangiolitic hepatitis was made, and a liver biopsy was performed on the 76th hospital day. On the 90th hospital day steroid therapy was instituted (Table 1). Within 5 days the total bilirubin had fallen from 8.7 to 4.61 mg. %, and within 12 days, to 2.4 mg. %. During this five-day period the stools became normal in color; the urine cleared of bile; the mild pruritus disappeared, and the appetite and feeling of well-being returned.

The patient was returned to the United States on Feb. 25 and admitted to Brooke Army Hospital on March 10, 1955, where the cortisone dosage was gradually decreased and discontinued after a total of 65 days. There were no ill effects from the steroids, except for moderate acne, a "moon face," and a trace of pretibial edema. He was discharged from the hospital April 3, 1955; one month later there was no evidence of residual liver disease.

TABLE 1.—*Case 1—Man, Aged Twenty-Five Years*

Hospital Day	Bilirubin, Mg. %			SBP %, Retention at 45 Min.	C. C. F., 48 Hr.	Cholesterol, Mg. %		Thymol Turbidity	Alk. Phosphatase, Bodansky Units	Intravenous Corticotropin Units/Day *	Intramuscular Cortisone, Mg/Day *	Liver Biopsy
	Direct	Indirect	Total			Total	Esters, %					
6	1.3	2.46	3.79		++			7.9				
13			6.4		+			9.7				
32			7.5					6.1	13			
39			8.6		0			5.8				
47			8.6		0			7.6				
55			9.9		0			5.8	15.2			
61	5.0	5.5	10.5		0				11			
62						132						
71	4.92	5.12	10.04		0	296	88	4.4	9.68			
74	4.29	4.51	8.8						10.2			
79	3.36	4.94	8.3		+	284	93	6.3	9.95			Yes
90	4.10	4.60	8.7		0			5.5	10.1	20		
93	3.98	3.24	7.22									
95	1.69	2.92	4.61									
97	1.69	2.15	3.84		0	268	70	5.3	7.5			
100										End	150	
102	0.91	1.49	2.40									
104											225	
109			1.60	16.8	0			5.2	7.5			
110											300	
122	0.28	0.61	0.89		0			7.1	5.6			
125	0.32	0.57	0.89	9.7	0	274	64	5.9	4.9			Yes
134											200	
145												Yes
147	0.2	0.4	0.6	5.0	++			6.5	6.3		150	
148											100	
150											50	
152											37.5	
153											25.0	
154											12.5	
156											End	
160	0.25	0.55	0.8	5.0	++			10.0	5.7			
190 †	0.21	0.24	0.45	4.0	+			4.0	3.4			

* Dose continued each day until increased, decreased, or ended, as shown.
† Follow-up studies.

Initial liver biopsy on the 76th hospital day showed preservation of liver architecture. The most conspicuous sign of liver disease was severe cholestasis. This appeared to be restricted to the canaliculi of the central portions of lobules, many being distended with bile plugs. On examination of numerous sections, somewhat inconspicuous evidence of parenchymal damage, with regeneration, was seen. There were swollen cells, polyploidia, and occasional deeply stained eosinophilic cells with pyknotic nuclei. Sporadic, small collections of leukocytes were present in the parenchyma. The periportal tissues also showed an increase in leukocytes, many segmented; a few eosinophils were evident. Masson stain demonstrated a slight increase of fibrous tissue in the periportal areas.

Repeat biopsy, after 35 days of steroid therapy, demonstrated only slight evidence of inflammation. Small infiltrates of round cells were present in most portal areas but rarely in the lobular parenchyma. There was mild cholestasis, limited to canaliculi of the central areas. The only other conspicuous feature was the active regeneration of liver cells, many showing three or four nuclei and mild fatty metamorphosis. On comparison with the previous biopsy, the changes were of the same nature but strikingly less in degree. A final liver biopsy, at the completion of 65 days of steroid therapy, revealed further diminution of the inflammatory cellular reaction and clearing of the cholestasis. The liver cells appeared to be rich in glycogen, with only occasional foci of fat-laden cells.

CASE 2.—A 25-year-old white man was admitted to a station hospital on July 12, 1955, and transferred to the Second General Hospital 55 days later. The day prior to admission he noted persistent, moderately sharp, right upper quadrant pain, accompanied by anorexia, nausea, and vomiting. On admission he complained of scleral icterus, dark

TABLE 2.—*Case 2—Man, Aged Twenty-Five Years*

Hospital Day	Bilirubin, Mg. %			SBP %, Retention at 45 Min.	C. C. F., 48 Hr.	Cholesterol, Mg. %		Thymol Turbidity	Alk. Phosphatase, Bodansky Units	Urine Urobilinogen, Mg./24 Hr.	Oral Cortisone Mg./Day *	Intramuscular Corticotropin, Units/Day *	Liver Biopsy
	Direct	Indirect	Total			Total	Esters, %						
1	1.75	2.15	3.90		0	236	49	3.75	8				
10			12.4					6	13.8				
25			16.2		0			5	9.4				
35			17.8			278	54	4	9	Neg. 1:20			
44	8.8	9.8	18.6		0			4		Neg. 1:1			
60													Yes
61	7.24	8.94	16.18		0	384	50	3.4	20.0		300		
62										9.5			
64											200		
66	2.12	3.66	5.78		0			2.8	12.7				
73	0.88	1.62	2.50			324	52	3.1	7.3	19			
80	0.65	1.37	2.02	6.2	0				6.9	25			
87	0.36	0.92	1.28	4.6	0	260	72	2.9	5.6				
89											150		
94	0.32	0.78	1.1										
99	0.28	0.52	0.80						8.65	0.2	75		
103											50		
108											37.5		
110	0.17	0.55	0.72	2.0	0	252	64	6.7	6.7	0.62			
111											25.5	80	
113											12.5	60	
114											End	40	
116												20	
117												End	
120													Yes
135	0.21	0.44	0.65	3.2	0	216	63	4.8	5.6				
240 †													Yes
267 †	0.02	0.41	0.43	2.0	0	267	73	5.5	0.74	3.2			
607 †	0.08	0.36	0.44	2.5	0	217	70	4.2	3.1	1.4			

* Dose continued each day until increased, decreased, or ended, as shown.
† Follow-up studies.

urine, and light stools, There was no known exposure to hepatotoxins, and his alcoholic intake was minimal.

Physical examination was within normal limits, except for mild icterus and a tender liver palpable 3 cm. below the right costal margin. Serial liver-function studies throughout his hospital stay are recorded in Table 2. Serial prothrombin times and serum proteins were normal; the urine was persistently positive for bile.

The hospital course over the next two months was complicated by persistent anorexia and a weight loss of 25 lb. Liver tenderness and enlargement remained unchanged. During the second week of hospitalization generalized pruritus developed, which was unresponsive to all forms of symptomatic therapy. A clinical diagnosis of probable cholangiolitic hepatitis was entertained, and liver biopsy was performed on the 60th hospital day. The following day steroid therapy was given, as recorded in Table 2. Within five days the total bilirubin fell from 16.2 to 5.78 mg. % (Fig. 1). Within a week, stools returned to normal color; bile disappeared from the urine, and the severe pruritus and anorexia disappeared. The 24-hour urinary urobilinogen rose within 24 hours to 9.5 mg. %, eventually increasing to 25 mg. % by the 19th therapy day.

The development of a "moon face" and slight acne were the only side-effects of steroids. Two weeks after therapy was discontinued there was no hepatomegaly; liver-function studies were normal. Reexaminations 4.5 months and 15 months after discharge disclosed no evidence of residual liver disease. An oral cholecystogram demonstrated a normal-functioning gallbladder.

Liver biopsy on the 60th hospital day, the day prior to institution of steroid therapy, revealed marked bile retention within the canaliculi of the central and midportions of the lobules. Bile stasis had reached the point where structures resembling bile lakes had been formed. In the parenchyma there were a few foci of necrosis and occasional inflammatory infiltrates. The inflammatory cells were a mixture of round cells and polymorphonuclear leukocytes. Some acidophilic cells and re-

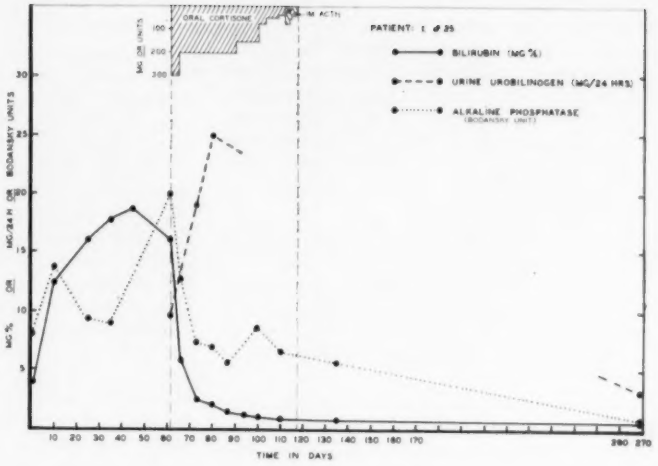

Fig. 1. — Note the prompt decline in the serum bilirubin and alkaline phosphatase with steroid therapy. There was also a rapid increase in the 24-hour urine urobilinogen. (Case 2)

generative activity were noted. The periportal fields showed slight bile duct proliferation and a moderate degree of inflammatory infiltrate and edema. There was some degeneration of primary bile duct epithelium but no bile thrombi or dilatation of the bile ducts.

Repeat biopsy, after completion of 56 days of steroid therapy, demonstrated greatly diminished

TABLE 3.—*Case 3—Man, Aged Twenty-Five Years*

Hospital Day	Bilirubin, Mg. %			SBP %, Retention at 45 Min.	C. C. F., 48 Hr.	Cholesterol, Mg. %		Thymol Turbidity	Alk. Phosphatase, Bodansky Units	Urine Urobilinogen, Mg./24 Hr.	Oral Cortisone Mg./Day *	Intramuscular Corticotropin, Units/Day *	Liver Biopsy
	Direct	Indirect	Total			Total	Esters, %						
2	6.6	0.4	7.0		0	321	65	2.0	16	Neg. 1:1			
9	9.4	1.1	10.5		0			6.5	15.9				
14	11.5	1.4	12.9		0	393	57	6.0	23	Neg. 1:1			
27	7.0	6.3	13.3		0			5.0	24	2.2			
31													Yes
38	13.5	11.6	25.1		0	220			23	5.2	300		
39	10.2	12.2	22.4										
41	6.2	8.6	14.8		0	274	46	5.9	15	15.2			
43	4.2	6.1	10.3										
46	2.9	4.1	7.0										
48	2.1	3.7	5.8		0	413	63	4.4	8.9	16.1			
55	1.1	2.0	3.1		0	272	66	8.7	5.7	7.6			
60											200		
62	0.7	2.0	2.7		0	234	67	6.7	7.7	9.6			
69	1.5	0.7	2.2		0	261	72	7.9	4.1		150		
75											100		
76	0.3	0.8	1.1	1.8	0	239	69	7.5	3.4				
80											50		
83	0.2	0.8	1.0	2.8	0	187	64	8.7	5.4				
85											25		
89													Yes
90	0.2	0.7	0.9	4.0	0			5.2	5.4	3.3			
92											End		
93												25	
97	0.2	0.3	0.5	1.8	0	180	73		5.4	3.8		End	
112	0.2	0.31	0.51	2.8	0	168	75	8.2	4.9	3.3			
159 †	0.2	0.4	0.6	3.3	+			4.2	3.4				Yes

* Dose continued each day until increased, decreased, or ended, as shown.
† Follow-up studies.

intracanalicular bile retention and inflammation. Occasional small foci of necrotic liver cells and pigment-laden histiocytes were found. The periportal fields showed slight bile duct proliferation and inflammatory-cell infiltrates. There was a moderate degree of fatty metamorphosis; the liver cells were rich in glycogen. Four months after completion of steroid therapy, a liver biopsy revealed only slight periportal fibrosis with a few chronic inflammatory cells.

CASE 3.—A 25-year-old white man was admitted to the Second General Hospital on Jan. 20, 1956, with a four-day history of jaundice, dark urine, and light stools. One week prior to admission he noted mild, bilateral, dull flank pain. There was no known exposure to hepatotoxins; alcoholic intake was minimal.

The only significant findings were moderate jaundice and slight tenderness in the right flank; liver and spleen were not palpable. Routine laboratory studies were normal. An oral cholecystogram on the fourth hospital day demonstrated faint visualization of the gallbladder, with no evidence of calculi. Serial liver-function studies are recorded in Table 3. The urine was consistently positive for bile, and the 24-hour urobilinogen was 13 Ehrlich units per 100 gm. of feces as late as the 36th hospital day. The serum proteins, A/G ratio, and prothrombin times remained normal.

Throughout his hospital course he was afebrile. The liver and spleen never became palpable. On the 15th day severe generalized pruritus developed, which was unresponsive to symptomatic therapy. A diagnosis of probable cholangiolitic hepatitis was made because of the typical biochemical abnormalities of regurgitation jaundice in a relatively asymptomatic young man. A liver biopsy was performed on the 31st hospital day. On the 38th hospital day steroid therapy was initiated and given, as shown in Table 3.

With treatment the jaundice and pruritus cleared with striking rapidity; there was prompt and progressive improvement in liver-function tests (Fig. 2). Within three days stools returned to normal color; the 24-hour urobilinogen rose to 130 Ehrlich units per 100 gm. of feces, and the bilirubinuria cleared. Except for moderate acne and a "moon face," there were no side-effects. Two and one-half weeks after therapy was discontinued there was no sign of relapse, and he was returned to duty. Reevaluation two months later showed no evidence of liver disease.

Initial liver biopsy on the 31st hospital day disclosed normal architecture. There was pronounced biliary stasis with inspissated bile in small canaliculi of central lobular areas. In portal regions there were slightly increased fibrosis and edema with moderate infiltration by chronic inflammatory cells; bile ducts were normal except for slight proliferation. Liver cells did not show frank necrosis, but occasional cells had large, bizarre, deep-staining double or triple nuclei. There were a few inflammatory cells scattered through the liver parenchyma.

A repeat liver biopsy at completion of steroid therapy revealed greatly reduced portal inflammatory infiltrate and bile stasis in contrast to the previous biopsy. A rare eosinophilic hepatic cell and occasional foci of necrosis were found. The outstanding features were regeneration and nuclear unrest, giant hyperchromatic nuclei, and double nucleation. This biopsy specimen differed little from any other type of late, healing hepatitis. A final liver biopsy, two months later, showed further improvement with only minimal periportal infiltrate and central lobular bile stasis.

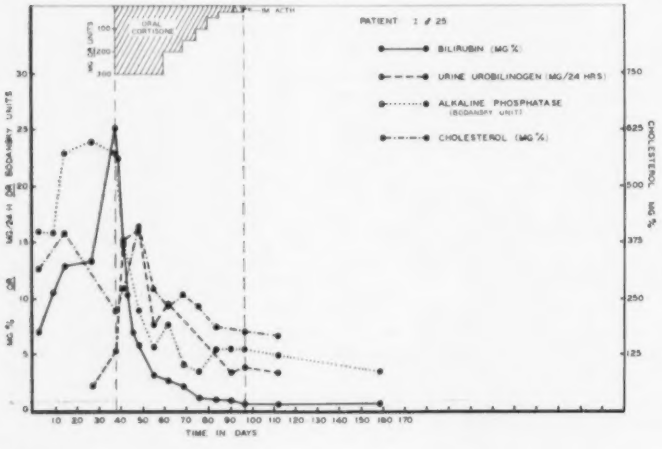

Fig. 2.—There was a prompt and rapid decline of the serum bilirubin, alkaline phosphatase, and total cholesterol. In contradistinction, the 24-hour urine urobilinogen rapidly increased. (Case 3)

TABLE 4.—*Case 4—Man, Aged Twenty-Seven Years*

Hospital Day	Bilirubin, Mg. %			SBP %, Retention at 45 Min.	C. C. F., 48 Hr.	Cholesterol, Mg. %		Thymol Turbidity	Alk. Phosphatase, Bodansky Units	Urine Urobilinogen, Mg/24 Hr.	Oral Delta-Cortisone Mg/Day *	Intramuscular Corticotropin, Units/Day *	Liver Biopsy
	Direct	Indirect	Total			Total	Esters, %						
7	6.8	7.6	14.4		0			5		Pos. 1:10			
14					0			4		0			
21	12.6	1.9	14.5			424	39		24.5				
28			18.0					4					
36			22.4		0	513	48	4	31.1				
43	11.6	14.2	25.8		0			5.9		Pos. 1:10			
48	14.9	14.8	29.7		0	612		7.9	32	5.9			
50													Yes
54											60		
55	12.0	19.3	31.3						32				
57	5.6	9.8	15.4			658	49	7.1	32	3.6			
60	2.0	6.4	8.4						30				
62	1.9	4.7	6.6		0	550	44	9.2	23	8.1			
64	1.5	4.1	5.6						21.6				
67	2.2	2.4	4.6						16.0				
69	1.1	3.1	4.2		0	485	73	8.7	12.7	6.3			
75	1.6	1.8	3.4			310	74	8.3	10.5	4.7			
83	0.56	1.27	1.83		0	258	71	7.9	5.7	5.7	30		
90	0.13	0.83	0.96	3.4		274	72	13	6.1	7.0			
92	0.28	1.04	1.32						4.2				
97	0.36	0.66	1.02		0	248	71	9	3.9	0.86	15		
99	0.36	0.74	1.10	4.2	0	258	70	3.7	3.3				
102	0.28	0.61	0.89						5.2		10		
104	0.24	0.72	0.96	3.4	0	216	60	3.4	3.3	3.5			
109	0.17	0.48	0.65						3.0	1.1	End	120	
114												End	Yes
119	0.13	0.46	0.59	3.2	0	252	68	3.0	4.4				
133	0.17	0.42	0.59	4.6	0	164	55	3.7	3.1	3.9			
197 †	0.12	0.28	0.40	3.5	0	174	65	2.6	3.0	2.1			Yes
441 †	0.10	0.72	0.82	0.4	0	225	60	2.0	2.7				

* Dose continued each day until increased, decreased, or ended, as shown.
† Follow-up studies.

CASE 4.—This 27-year-old white man was admitted to the Second General Hospital on March 16, 1956, with anorexia, generalized malaise, and mild, right upper quadrant tenderness of one week's duration. The day before admission his urine became dark and his eyes icteric. There was no history of exposure to hepatotoxins, and the alcoholic intake was minimal. Past history indicated that he had always been in excellent health except for a duodenal ulcer 1 year earlier; he had been asymptomatic for 10 months. A gastrointestinal series six months prior to admission was said to be normal.

The only significant physical findings were mild scleral icterus and a tender, firm liver palpable 2 cm. below the right costal margin. Routine laboratory tests were normal. Serial liver-function studies are shown in Table 4. The serum proteins, prothrombin time, gastrointestinal series, and "scout" film of the abdomen were normal.

Over the next month he remained afebrile but experienced continued anorexia, pruritus, intermittent lower abdominal cramps, and moderate, dull, right upper quadrant pain. The jaundice increased; the stools became light in color, and the urine was consistently positive for bile. Daily intravenous dextrose was necessary. There was a 30 lb. weight loss. On the 48th hospital day the urobilinogen was only 11 Ehrlich units per 100 gm. of feces. From the clinical course and biochemical abnormalities a diagnosis of probable cholangiolitic hepatitis was made. A liver biopsy was performed on the 50th hospital day. On the 54th day steroid therapy was given, as shown in Table 4. There was prompt improvement in well-being and in laboratory abnormalities (Fig. 3). Within 10 days the bilirubinuria cleared and stools returned to normal color, with fecal urobilinogen rising to 168 Ehrlich units per 100 gm. Except for moderate acne and a "moon face" there were no ill effects. Throughout this period he was given antacids and an ulcer diet, supplemented with 6 gm. of potassium chloride daily. Three weeks after completion of therapy there was no evidence of

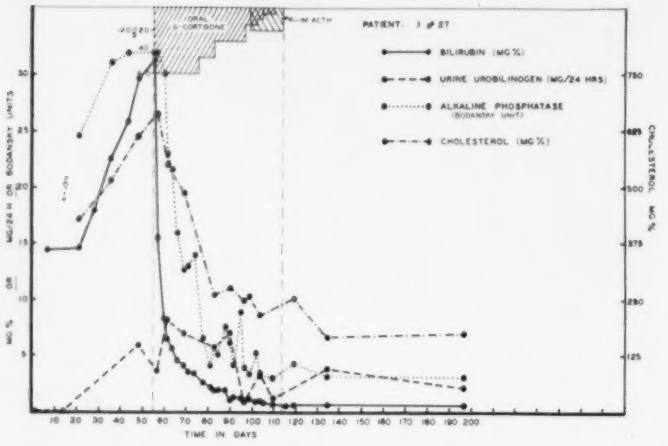

Fig. 3.—As in the previous case, there was a rapid decline in the serum bilirubin, cholesterol, and alkaline phosphatase. There also was a modest increase in the 24-hour urine urobilinogen. (Case 4)

liver disease, and his weight had returned to normal. On reevaluation 3 and 10 months later, he was asymptomatic, with no clinical or laboratory indication of residual liver disease.

Initial liver biopsy on the 50th hospital day failed to disclose significant changes in the general architecture. However, the portal areas exhibited minimal infiltration by lymphocytes, neutrophils, and eosinophils. There was moderate proliferation of interlobular bile ducts. Bile stasis was seen predominately in central lobular areas. Hepatic cells were slightly swollen, with eosinophilic, granular cytoplasm and fairly regular, even-staining nuclei. There were occasional foci of necrosis and inflammatory infiltrates within the liver parenchyma.

Liver biopsy at completion of steroid therapy revealed marked clearing of bile stasis, diminution in the inflammatory exudate, slight fibrosis in portal areas, and focal areas of minimal fatty metamorphosis. Final biopsy three months after therapy showed increase in liver-cell size, probably due to increased glycogen. Fatty metamorphosis, inflammatory infiltration, reactive pleomorphism, and bile duct proliferation were slight.

Comment

Historical data in these cases are suggestive of hepatitis. It is well to reemphasize that a careful history is still the most important tool in differentiating causes of jaundice. In each case the age of the patient favored hepatitis. However, even in a young person, painless jaundice from a common duct obstruction can occur.[18] In older patients, the probability of obstruction from tumor or stone is greater, but hepatitis can be the cause. In the cases presented, the minimal prodromata and the absence of fever and leukocytosis were more characteristic of the cholangiolitic form of hepatitis. Jaundice, dark urine, light stools, pruritus, anorexia, weight loss, hepatomegaly, and skin excoriations were the outstanding clinical features of these cases. Splenomegaly, which would be more suggestive of intrahepatic pathology, was not present in any of these patients.

The laboratory findings were those of prolonged regurgitation jaundice. In the early stages of hepatitis there often is a brief phase of functional obstruction in addition to the evidence of hepatocellular damage. Steigmann and Popper[19] found some degree of reduced bile flow in 26% of 79 cases of acute catarrhal hepatitis. Complete obstruction was demonstrated for 2 to 30 days in 10%. It is when the obstructive phase persists, accompanied by biochemical and clinical features of regurgitation jaundice, that confusion can arise as to the site of obstruction. The recently developed serum glutamic oxalacetic transaminase test has not resolved this problem. A modest increase in transaminase activity occurs in both biliary obstruction and cholangiolitic hepatitis.[20]

The advantages of liver biopsy in evaluation of liver disease are well known, as are its limitations. In our cases, the histological features of the initial biopsies, performed 30 to 75 days after onset of illness, were similar to changes described by earlier authors.[2,7,12,16,17,19,21,22] The most distinctive feature was marked cholestasis with preservation of hepatic architecture. Canaliculi of central portions of lobules were distended with bile plugs, and periportal areas showed inflammatory cells, but no distention or bile stasis in peripheral or periportal bile radicles was noted. Cellular changes were inconspicuous, and, on the basis of initial biopsies, it was difficult to differentiate viral hepatitis from extrahepatic obstruction. In this respect, Dubin [23] compared liver biopsy specimens of 83 cases of obstructive jaundice with those of 30 cases of cholangiolitic hepatitis in which no obstruction was found at an exploratory laparotomy and estimated that in about 70% of these cases one should be able to distinguish between these two entities. He found that the diagnostic features of extrahepatic obstruction, consisting of bile lakes, bile granulomas, and exudate within the lumen of intrahepatic bile ducts, did not appear before the fourth week of clinical jaundice. Unfortunately, these changes occurred only infrequently, and the early onset of pericholangitis, with centrolobular focal necrosis and inflammation in the obstructive jaundice cases, further simulated cholangiolitic hepatitis. However, it was noted that in extrahepatic obstructive jaundice focal necrosis tended to be limited to areas of bile stasis, while in cholangiolitic hepatitis the necrosis occurred haphazardly, and bile plugs tended to be fewer and smaller.

The reason for the apparent involvement of the cholangiolar system with prominant clinical and biochemical features of obstruction is unknown. Steigmann and Popper [19] suggested that regurgitation could be the result of compression by inflammatory exudate of the canals of Herring, the delicate links between the intralobular biliary canaliculi and the primary bile ducts. However, Watson and Hoffbauer [2] noted that this periportal reaction did not appear to be of sufficient magnitude to be the sole cause of obstruction and suggested that the causative agent injures the cholangiole, resulting in increased permeability, with diapedesis of bile into the lymphatics. The bile thrombi could then be the result of a secondary inspissation phenomenon, since relatively more water and less solids would migrate through the injured cholangiole. Another possibility is the selective failure of bile secretion by the injured liver cell.

The features of the four cases presented were very similar to those of primary intrahepatic cholestasis following exposure to the chemical agents mentioned earlier. In the absence of such exposure, the virus of infectious hepatitis was the most likely cause. Unfortunately, lack of a specific test makes this a diagnosis of exclusion. More recently Popper and Szanto [21] have summarized this problem and stated:

> Intrahepatic cholestasis is a response of the hepatic parenchyma to injury of any kind. It may be a component in various hepatic diseases exhibiting hepatocellular damage such as viral hepatitis as well as postnecrotic and septal (e. g., nutritional) cirrhosis. It may also be the sole manifestation of liver disease with jaundice, not necessarily associated with liver cell damage, and may be seen in patients following exposure to various drugs, or without established etiology.

Similarly Dubin,[23] in a study of a large group of viral hepatitis cases, has noted a broad spectrum of histological changes, varying from diffuse parenchymal infiltration to the histological picture of cholangiolitic hepatitis similar to our presented cases. Between these two contrasting pictures there were many cases that presented a mixture of all of these histological features.

Steroid therapy in our cases was initiated relatively late in the illness, after it became apparent that a spontaneous remission in the near future was improbable. The large initial daily dosage of steroids was specifically chosen in the hope that their diagnostic and therapeutic effect would be clearly defined. The dosage was continued

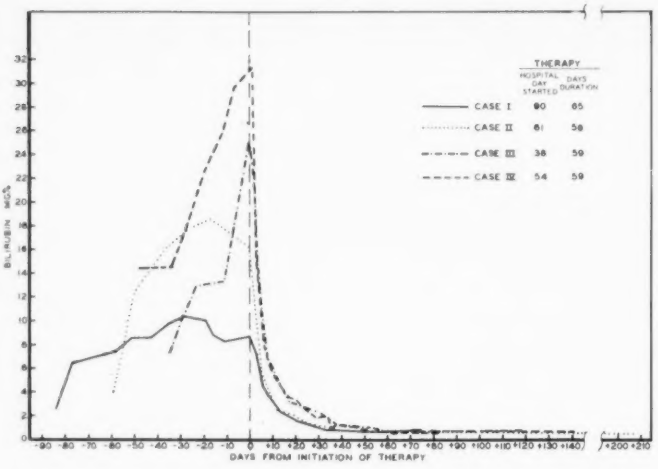

Fig. 4.—Note the effect of steroids on the serum bilirubin. There was a 47% to 69% decrease within 4 days and approximately a 75% fall after 10 days. From this point, there was a gradual decline, with no increase in serum bilirubin after discontinuance of steroid therapy.

until an arbitrary level of 2 mg. % or less of serum bilirubin was reached; this occurred within 20 to 30 days. Thereafter the dosage was slowly decreased over the next three to four weeks to complete a two-month course. Throughout this period these patients were on low-sodium diets, supplemented with oral potassium choloride, 4 to 6 gm. daily. Except for the expected "Cushingoid" appearance, there were no complications.

The serum bilirubin fell rapidly at onset of therapy, followed by a gradual return to normal. This response, as shown in Figure 4, was similar to that described by Evans et al.[3] in parenchymal hepatitis; e. g., at least a 50% reduction of total bilirubin within 5 days and approximately a 75% drop at the end of 12 days. The abnormal cholesterol and alkaline phosphatase reverted toward normal in a prompt but less dramatic fashion. The severe pruritus subsided; bilirubinuria cleared, and stools returned to a normal color within a week. More definitely, the improvement in bile flow was reflected by the prompt increase in 24-hour urine and fecal urobilinogen. On completion of steroid therapy, each patient was asymptomatic and biochemical abnormalities had reverted to normal. Of equal importance was the significant decrease in cholestasis and periportal inflammatory reaction in the liver biopsy specimen. Limited follow-up observations have revealed no evidence of chronic liver disease.

Chalmers et al.[23] have evaluated serum bilirubin response to steroid therapy in proven extrahepatic obstruction as well as in parenchymal hepatic disease. A four-day course of repository corticotropin injection (ACTH Gel), 40 units every 12 hours, was given to 41 jaundiced patients. The response was calculated by expressing the average drop from control levels on the two days after cessation of corticotropin as a percentage of control values; 65% of the hepatitis patients, 12.5% of the cirrhotic patients, and 10% of the patients with extrahepatic obstruction had a serum bilirubin drop of 50% or greater. These authors concluded that as a diagnostic test the degree and rapidity of fall of the total serum bilirubin had limited usefulness, since patients with hepatitis might not respond, and patients with extrahepatic obstruction occasionally would. This test is no more infallible than any other procedure used in the differential diagnosis of jaundice. Nevertheless, serum bilirubin decreases of 47%, 64%, 59%, and 69% in our four patients after four days of steroid therapy made the diagnosis of cholangiolitic hepatitis more probable. Their

use in this manner should be limited to carefully selected cases.

The rapid clinical and biochemical responses to steroids can not readily be explained by increase in appetite or increased liver glycogen storage induced by steroids.[25] Patterson et al.[26] demonstrated a choleretic action of cortisone in normal subjects and in patients with various alimentary tract disorders, including one patient with viral hepatitis, one with nonfunctioning gallbladder, and another with a postcholecystectomy syndrome. However, Shay and Sun [27] were unable to demonstrate a hydrocholeretic or choleretic action of hydrocortisone. In evaluating the four-day corticotropin test in three cases of extrahepatic obstruction, Chalmers et al.[24,28] noted that the serum bilirubin levels dropped by more than one-third, without increase in urine urobilinogen. This suggested that there may be an alteration in the usual pathway of bilirubin metabolism in addition to a reduction of intrahepatic inflammatory reaction. Information obtained during the clinical course of our four patients does not lend itself directly to further clarification of these discrepancies. However, the rapid decrease in intrahepatic cholestasis was most likely due to the anti-inflammatory effect of steroids.

Summary

Among 722 cases of infectious hepatitis, there were only 4 patients in whom a diagnosis of cholangiolitic hepatitis was appropriate. These patients were young men with no history of drug ingestion or excessive alchohol intake. Their clinical course was characterized by progressive protracted jaundice, moderate anorexia, severe pruritus, and moderate weight loss. Serial liver-function studies revealed hyperbilirubinemia, bilirubinuria, low urinary and fecal urobilinogen, and elevated alkaline phosphatase and total cholesterol. In contrast, cephalin-flocculation and thymol-turbidity tests were relatively normal. The histological counterpart of cholangiolitic hepatitis was present in liver biopsy specimens obtained from one to two and one-half months after the onset of symptoms. The differential diagnosis presented a problem, inasmuch as similar clinical, laboratory, and histological changes may be seen in extrahepatic obstruction.

Oral cortisone, 200-300 mg., or equivalent intravenous corticotropin (ACTH) or oral prednisone were used one to three months after onset of symptoms in the four cases. There was prompt return of appetite and well-being. After four days of steroids the total serum bilirubin decrease ranged from 47% to 69%. This rapid decline was helpful in establishing the diagnosis of cholangiolitic hepatitis as opposed to extrahepatic obstruction. Bilirubinuria, acholic stools, and pruritus cleared within 7 to 10 days. The rise in the urine and fecal urobilinogen was further evidence of the decrease of intrahepatic obstruction. After 20 to 30 days, the serum bilirubin had fallen to approximately 2 mg. % and the steroid doses were gradually decreased over the ensuing three to four weeks. At completion of approximately two months of therapy the clinical and biochemical abnormalities had reverted to normal. Serial liver biopsies demonstrated a striking regression of cholestasis and periportal inflammation.

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The Erythropoietic Factor in Hypoxic Patients With Emphysema Without Secondary Polycythemia

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Many patients with chronic hypoxia due to pulmonary emphysema fail to develop a secondary polycythemia.[1,2] When polycythemia does occur in such patients it is often less than that which a normal person would develop if exposed to a similar degree of hypoxia.[3] Many have sought an explanation for this unresponsiveness of the emphysematous patient to the hypoxic stimulus. There is agreement that some emphysematous patients fail to develop polycythemia owing to a failure of erythropoiesis.[2] Although such patients frequently have chronic pulmonary infections, a critical study of their hemopoietic dynamics does not yield information similar to that found in the anemia of infection.[2,4] There is increasing evidence to suggest that the hypoxic stimulus to erythropoiesis is mediated by a humoral factor, erythropoietin.[5-7] The biological assay of this humoral factor in the plasma of unresponsive patients with emphysema has not been documented.

The present report is concerned with the assay for erythropoietin activity in the plasma from hypoxic and emphysematous patients who have failed to develop secondary polycythemia. The work was carried out in an attempt to answer the following question: Do patients with pulmonary emphysema, hypoxia, and no compensatory polycythemia show levels of circulating erythropoietins different from those observed in normal subjects?

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From the Radioisotope Service and Department of Medicine, Veterans Administration Hospital, and the University of Oklahoma School of Medicine and Hospitals, Oklahoma City.

Clinical Material and Experimental Methods

Five patients with pulmonary emphysema and hypoxia served as donors for the experimental plasma. The pertinent laboratory data obtained in these patients are presented in Table 1. Pulmonary function studies in each of these patients supported the diagnosis of obstructive emphysema. It should be noted that in each of these patients the observed hemoglobin value was distinctly below what would

TABLE 1.—*Hypoxic Donor Patients*

Patient	Age, Yr.	Hgb., Gm. %	Predicted Hgb. * Gm. %	Arterial O_2 Saturation in Room Air, %	Vital Capacity, % of Predicted †	1-Sec. Vital Capacity, % of Total	Maximum Breathing Capacity, % of Predicted †	N. P. N., Mg. %	BSP, % Retention	Stool Blood
1	57	14.0	19.7	84.7	72	38	28	27	2	Neg.
2	56	15.2	17.6	87.0	46	32	19	23	5	Neg.
3 ‡	60	14.1	20.0	84.0	84	34	—	20	15	Pos.
4	70	14.9	19.7	84.8	76	35	27	20	5	Neg.
5	46	14.6	20.0	84.0	57	34	29	30	3	Neg.

* Predicted value for patients at altitude with comparable degree of hypoxia.[8]

† Predicted value for each patient calculated by the method of Comroe.[11]

‡ Arterial oxygen values determined 2 months after plasma donation.

be expected in a normal person chronically exposed to a similar degree of anoxia.[8] In no patient was there clinical evidence of an active inflammatory process. Control plasmas were obtained from two young men who were in vigorous good health.

Blood was obtained from the patients and the normal subjects in an identical fashion. All plasmas were processed identically. From each donor 400-500 ml. of venous blood was anticoagulated with 120 ml. of A. C. D. solution in Baxter Transfuso Vac glass bottles. The blood was centrifuged at 2,000 rpm for one hour and the supernatant plasma removed and stored in a frozen state until processed. Each aliquot of plasma was processed and assayed separately. The plasma was thawed at room temperature and its pH adjusted to 5.5 with the addition of appropriate amounts of 1 N HCl. The plasma was placed in a 250 ml. flask and immersed in a boiling water bath. With constant mechanical stirring, the plasma was heated for a time sufficient to maintain its temperature at 98 C for 10 minutes. It was cooled to room temperature and centrifuged. The supernatant fluid was removed and retained. The coagulum was thoroughly washed twice in volumes of redistilled water equal to the original volume. The supernatant fluid and the water from both coagulum washes were pooled. This pool was dialyzed, first against tap water for 12 hours and then against distilled water for 6 hours. The nondialyzable fraction was subjected to lyophilization and stored until immediately prior to testing. It was then reconstituted to the original volume of plasma by use of sterile pyrogen-free water. This solution will be referred to as the plasma filtrate.

The method of assay for the erythropoietic activity of the plasma filtrate was as follows: The assay animals were mature male Sprague-Dawley rats weighing from 180 to 200 gm. All animals were fed ad libitum and weighed every third day during the experimental period. Each animal was given daily injections with the plasma filtrate for 13 consecutive days. The injections were intraperitoneal. The daily dose of plasma filtrate was equal to 2% of the animal's current weight. All animals continued to gain weight throughout the experimental period.

The indices of erythropoiesis studied in the assay animals included estimations of the hemoglobin, the hematocrit, and the erythrocyte and reticulocyte counts. All bloods were obtained from a tail vein, and precaution was exercised against excessive blood loss. Hemoglobins were determined by the cyanmethemoglobin method.[8] A microhematocrit technique was used. Erythrocyte counts were done with use of duplicate pipettes and duplicate counting chambers. The reticulocytes were stained with brilliant cresyl blue, counterstained with Wright's stain, and counted. The reticulocyte counts were expressed as a per cent and estimated by a count of 1,000 erythrocytes.

TABLE 2.—*Hemoglobin Values of Animals Given Injections*

Donor Substance	Animals, No.	Mean Hgb., Gm. % Day 0	Mean Hgb., Gm. % Day 14	Mean Hgb., Difference Days-0 & 14
Hypoxic plasma filtrate				
1	3	13.4	14.2	+0.8
2	3	13.3	14.8	+1.5
3	2	12.3	14.3	+2.0
4	4	12.8	14.4	+1.6
5	4	13.5	13.7 *	+0.2
Normal plasma filtrate				
1	4	13.3	12.9	−0.4
2	4	12.6	12.7	+0.1
Saline				
1	5	13.9	14.0	+0.1
2	3	13.1	13.1	0

* One observation deleted owing to excessive bleeding (N=3)

Results

The hematological responses of groups of rats to the daily intraperitoneal injection of various plasma filtrates and of saline are presented in Tables 2, 3, and 4. The blood values obtained immediately prior to the first injection are referred to as Day 0; those obtained at the end of the experimental period are tabulated as Day 14 values. The erythrocyte counts, hematocrit, and reticulocyte counts were determined and are expressed in the tables as

TABLE 3.—*Erythrocyte Values of Animals Given Injections*

Donor Substance	Animals, No.	Mean, RBC × 10^6 Day 0	Mean, RBC × 10^6 Day 14	Difference Day 0 and Day 14
Hypoxic plasma filtrate				
1	3	5.99	7.47	+1.48
2	3	5.85	6.87	+1.02
3	2	6.36	7.15	+0.79
4	4	6.08	7.22	+1.14
5	4	6.33	6.41 *	+0.08
Normal plasma filtrate				
1	4	5.79	5.91	+0.12
2	4	6.16	5.80	−0.36
Saline				
1	5	5.39	6.79	+1.40
2	3	6.70	6.10	−0.60

* One observation deleted owing to excessive bleeding (N=3).

TABLE 4.—*Hematocrit Values of Animals Given Injections*

Donor Substance	Animals, No.	Mean Hematocrit, % Packed RBC		
		Day 0	Day 14	Difference Day 0 and Day 14
Hypoxic plasma filtrate				
1	3	47.2	54.0	+6.8
2	3	46.0	53.5	+7.5
3	2	47.3	48.5	+1.2
4	4	46.4	48.0	+1.6
5	4	45.9	45.7 *	−0.2
Normal plasma filtrate				
1	4	46.2	50.1	+3.9
2	4	45.3	42.8	−2.5
Saline				
1	5	46.1	50.5	+4.4
2	3	47.5	45.7	−1.8

* One observation deleted owing to excessive bleeding ($N=3$).

TABLE 5.—*Reticulocyte Values of Animals Given Injections*

Donor Substance	Animals, No.	Mean Reticulocytes, %		
		Day 0	Day 14	Difference Day 0 and Day 14
Hypoxic plasma filtrate				
1	3	6.3	4.7	−1.6
2	3	7.1	6.3	−0.8
3	2	6.0	4.5	−1.5
4	4	5.4	4.9	−0.5
5	4	5.6	4.1 *	−1.5
Normal plasma filtrate				
1	4	5.8	5.1	−0.7
2	4	4.5	5.4	+0.9
Saline				
1	5	4.7	4.4	−0.3
2	3	5.0	3.9	−1.1

* One observation deleted owing to excessive bleeding ($N=3$).

the mean for each group of animals receiving a test plasma filtrate. Each group of rats receiving hypoxic plasma filtrate showed a mean increase in hemoglobin values on the 14th day, as compared to the pretreatment level. Groups of rats receiving the normal plasma filtrate and saline showed a small and variable response. A similar trend was noted in the erythrocyte counts and hematocrits. However, the rats receiving the hypoxic plasma filtrate showed a decrease in the reticulocyte percentage on the 14th day.

These data were subjected to statistical analysis with use of "Student's" *t*-test for nonindependent samples.[9] By the method used, the mean of the individual differences during treatment is determined for each experimental group. The analysis indicates the probability that the mean is not zero. The results of these analyses are tabulated in Table 6. It is to be noted that the increases in hemoglobin and erythrocyte counts shown by the rats receiving hypoxic plasma filtrate were greater than those found in the control animals and that these differences are of significance statistically. Similarly the depressed reticulocyte counts shown by rats receiving hypoxic plasma filtrate were significant. The hematocrit values of the experimental groups show

TABLE 6.—*Significance of Values of the Mean Difference Between Day 0 and Day 14 for Hemoglobin, Erythrocyte Count, Hematocrit, and Reticulocyte Count of Animals Given Injections*

Laboratory Determination	Donor Substance	Day 0- Day 14, Mean Difference	*t*-Value *	*P*-Value
Hgb., gm. %	Hypoxic plasma filtrate	+1.22	4.026	<0.02
	&			
	control plasma or saline	−0.05	0.423	>0.60
RBC × 10^6	Hypoxic plasma filtrate	+0.90	3.887	<0.02
	&			
	control plasma or saline	+0.14	0.309	>0.80
Hct., %	Hypoxic plasma filtrate	+3.40	2.150	<0.10
	&			
	control plasma or saline	+1.00	0.546	>0.50
Reticulocytes, % of RBC	Hypoxic plasma filtrate	−1.18	5.300	<0.01
	&			
	control plasma or saline	−0.45	0.974	>0.30

* "Student's" *t*-test with nonindependent samples.[9]

only a trend toward an increase, when compared to the control animals.

Comment

The biological significance of erythropoietin and its chemical characterization, elaboration, and mode of action is still imperfectly understood[10] and will not be reviewed here. The experiments reported here employed a conventional rat assay method for estimating plasma erythropoietin activity. The results indicate that there are levels of erythropoietin in the plasma of hypoxic, emphysematous, and nonpolycythemic patients which are in excess of that found in normal plasma. The evidence for this is that all hypoxic plasma filtrates consistently produced an increase in hemoglobin and erythrocyte count. The injection of normal plasma filtrates or of saline produced variable changes. When these results were analyzed, only the increases after injection of hypoxic plasma filtrates were significant statistically.

The changes seen in the hematocrits were variable. It has been shown that boiling plasma for 10 minutes, as was done in the present study, destroys from 70% to 90% of its erythropoietic-stimulating activity.[11] Since our results in the control animals are consistent with those reported by others,[12] it is possible that significant changes in hematocrits would have been seen if erythropoietic activity had not been decreased by boiling.

No firm explanation can be offered for the apparent decrease in reticulocyte counts of the animals receiving hypoxic plasma filtrate. We have assumed that a reticulocytosis must have occurred to produce the increases found in the red cell counts. The decrease in the reticulocyte counts at the end of the experimental period suggests that the induced reticulocytosis has passed and that the duration of the stimulus is less than 24 hours. An alternate explanation is that the assay animals were becoming refractory to the hypoxic plasma filtrate.

These experiments present further evidence that the failure of emphysematous and hypoxic patients to develop the expected polycythemia results from a refractory bone marrow.

Summary

Experiments are presented which indicate that the plasma from patients who are hypoxic as a result of pulmonary emphysema but who have not developed secondary polycythemia contain quantities of erythropoietin greater than that seen in normal subjects.

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Leptospiral Meningitis

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In recent years there has been an increasing interest and awareness of the global significance of leptospiral infections. This subject was discussed in considerable detail in a Walter Reed Army Medical Center Symposium.[1]

The increasing incidence of leptospirosis in the United States, as recently reviewed,[2] is due more likely to a higher index of suspicion and improved diagnostic methods but undoubtedly represents only a fraction of the true prevalence of the disease.

The protean clinical features of human leptospirosis mimic a variety of diseases, covering a broad spectrum from mild flu-like signs to severe fulminant hepatic disease.[3]

Although meningeal involvement has been emphasized in previous reports,[3-13] aseptic meningitides caused by Leptospira are undoubtedly frequently not specifically diagnosed or suspected. This is particularly true when there is no associated icterus.

This report is concerned with 10 cases of leptospiral meningitis, diagnosed at University Hospital between 1954 and 1958. Only one of these patients was icteric. During the previous 10 years, that is, 1945 to 1954, only three cases of leptospirosis were diagnosed at this hospital, and two of the three patients were severely icteric. This situation suggests that leptospirosis is in all probability more prevalent here than previously suspected. The present study serves to illustrate the necessity for a high index of suspicion and adequate laboratory facilities to diagnose leptospiral meningitis. The microscopic agglutination test of Ward et al.,[14] employing killed antigens, was utilized throughout these studies.

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Report of Cases

CASE 1.—A 34-year-old unemployed white man from Columbus was admitted to University Hospital on Sept. 10, 1954, complaining of severe frontal and occipital headache and weakness of his legs of three days' duration. His illness began abruptly seven days before admission, when, while fishing in a local stream, he experienced a shaking chill followed by nausea, vomiting, fever, and headache. The following morning he had aching of his back and legs, which persisted for the next two days. He then noted increasing severity of his headache as well as weakness of his legs and a faint yellow tinge of his skin and eyes. These symptoms persisted until admission.

Physical examination on admission revealed a moderately ill lethargic man. Temperature was 97.8 F; pulse, 70; respirations, 22, and blood pressure, 110/70. The skin showed slight icterus. His sclerae and conjunctivae showed marked injection. The patient also exhibited marked nuchal rigidity, a positive tripod sign, and a positive Kernig's sign. There was weakness in both legs. His liver was felt 5 cm. below the right costal margin but was nontender.

The admission blood cell count showed 6,700 white blood cells per cubic millimeter, with 78% neutrophils, 19% lymphocytes, 2% eosinophils, and 1% basophils. Urine showed 10 to 15 white blood cells per high-power field. Blood urea nitrogen was 26.5 mg. %; van den Bergh, 2.5 mg. % direct and 3.5 mg. % total. Thymol turbidity was 20 mg. % (Kingsbury-Clark albumin standards; normal, <15 mg. %), and cephalin flocculation showed a trace. Prothrombin was 47.5%. Lumbar puncture revealed a clear fluid, with an opening pressure of 180 mm. (water) and closing pressure of 80 mm. The spinal fluid contained 472 white blood cells per cubic millimeter (all lymphocytes) and 61 red blood cells; protein was 64 mg. %; chlorides, 793 mg. %, and sugar 56 mg. % (blood sugar, 99 mg. %).

The patient remained afebrile throughout his hospital course. He received acetylsalicylic acid for his headache and was placed on 500 mg. of tetracycline every six hours. By the 4th hospital day he was asymptomatic, and when discharged on the 12th day he was no longer icteric or weak and showed no hepatomegaly.

All studies for virus encephalitides were negative, but his agglutination tests for Leptospira were as follows:

	Day of Illness	
	7	14
L. icterohaemorrhagiae	Pos. 1:40	Pos. 1:10,000
L. canicola	Neg.	Neg.
L. pomona	Neg.	Neg.

Comment.—Thus, the diagnosis of leptospiral jaundice with meningitis due to L. icterohaemorrhagiae was established. His infection was probably contracted in the area of the local creek he visited frequently in his fishing.

CASE 2.—A 50-year-old white railroad maintenance worker, from Sunbury, Ohio, was admitted to University Hospital on Dec. 7, 1955, with a one-week history of headache, progressive malaise, irritability, lethargy, and stiffness of his neck. Six days prior to admission he had chills and fever of 103.4 F. He was treated by his physician at this time with penicillin and sulfonamide, with little change in his condition. Four days prior to admission he noted the onset of extreme fatigue.

On admission his temperature was 102.4 F. The pertinent physical findings consisted of marked nuchal rigidity as well as positive Kernig and Brudzinski signs. No muscular weakness was detected. The liver was palpable at the right costal margin, and it was tender. No jaundice was present. His sclerae and conjunctivae were slightly injected, and he complained of photophobia. Initial white cell count was 12,500, with a normal differential.

Lumbar puncture on admission revealed a slightly hazy fluid under 116 mm. of (water) pressure. The fluid contained 10 red blood cells and 312 white blood cells (69% lymphocytes, 31% neutrophils); the protein was 82 mg. %; chlorides, 707 mg. %, and sugar, 58 mg. % (blood sugar, 123 mg. %). The van den Bergh was 0.7 mg. % direct and 1.2 mg. % total, and his sulfobromophthalein (Bromsulfalein) test (5 mg. of dye per kilogram of body weight) showed 37% retention after one hour; cephalin flocculation was negative. Blood urea nitrogen was 16 mg. %. A repeat lumbar puncture on his sixth hospital day showed an opening pressure of 135 mm. and revealed 23 white blood cells, 54 mg. % protein, 675 mg. % chlorides, and 43 mg. % sugar (blood sugar 100 mg. %). At this time his sulfobromophthalein showed 18% retention.

Treatment was entirely supportive. The patient improved gradually and became afebrile on the 10th hospital day. He was discharged on the 14th day, completely asymptomatic. All etiologic studies were negative at time of discharge, but follow-up studies revealed that his leptospiral agglutinations were as follows:

	Day of Illness	
	7	24
L. icterohaemorrhagiae	Neg.	Pos. 1:1,800
L. canicola	Neg.	Pos. 1:1,600
L. pomona	Neg.	Neg.

Comment.—This patient had frequent exposure and contact with animals, especially rats, in his job as a railroad yard worker.

CASE 3.—A 16-year-old white male student from Washington Court House, Ohio, was admitted to University Hospital on July 3, 1956, with a history of sudden onset of "sore back" three days prior to admission. Two days before admission he developed fever and marked lethargy, followed the next day by generalized weakness, severe headache, and stiff neck. He was seen by his family physician, who diagnosed his case as poliomyelitis and referred him to this hospital. Past history was insignificant except for the fact that he admitted to swimming in local streams. On admission his temperature was 104 F.; his pharynx was injected, and there was questionable weakness of his left leg. Neurologic examination was within normal limits. White blood cell count was 15,500, with 95% neutrophils, 4% lymphocytes, and 1% basophils. Cerebral spinal fluid examination at the time of admission showed an opening pressure of 155 mm. (water) and revealed no red or white blood cells; sugar was 79 mg. % (blood sugar, 126 mg. %), and protein, 30 mg. %. Repeat examination of spinal fluid, on the third hospital day, revealed 22 red and 140 white blood cells of which 97% were neutrophils and 3% lymphocytes; protein, chlorides, and sugar were normal. Serum van den Bergh was found to be 1.0 mg. % total, with a direct determination of 0.7 mg. %; cephalin was 2+; thymol turbidity, negative. On the second hospital day the patient developed marked conjunctival injection. Therapy included acetylsalicylic acid and penicillin. By the sixth day the patient became afebrile. No muscle weakness could be detected at this time, and the patient was discharged as well, on the ninth hospital day, with a tentative diagnosis of nonparalytic poliomyelitis.

Serologic tests for mumps, lymphocytic choriomeningitis, eastern equine encephalomyelitis, western equine encephalomyelitis, and St. Louis encephalitis were all negative. No enteric viruses were isolated from the stools. Serologic tests for leptospirosis were as follows:

	Day of Illness		
	10	13	16
L. icterohaemorrhagiae	Neg.	Neg.	Pos. 1:2,048
L. canicola	Neg.	Neg.	Neg.
L. pomona	Neg.	Pos. 1:512	Pos. 1:2,048

Comment.—The symptoms which the patient presented at the onset of his illness were strikingly similar to those seen in poliomyelitis. The serologic studies indicated that we were dealing with a leptospiral infection, either the icterohaemmorrhagiae or the pomona type. Later blood specimens may have delineated further the specific agent. Without leptospiral studies the diagnosis would probably have remained nonparalytic poliomyelitis.

Case 4.—An 18-year-old white male construction worker, from Columbus, Ohio, was admitted to University Hospital on July 7, 1956, with a history of sudden chills, fever, and stiff neck of 18 hours' duration. On the day of admission he developed dizziness, pharyngitis, and pain in the muscles of both thighs. No history of nausea or vomiting was noted. Past history was noncontributory except for the fact that he often swam in local streams and quarries. On admission his temperature was 103.8 F; pulse, 114; respirations, 20; blood pressure, 120/70. Positive physical findings included minimal conjunctival and mild pharyngeal injection. He exhibited moderate nuchal rigidity and stiffness in the back and hamstring muscles but no weakness. White blood cell count on admission was 15,500, with a normal differential. Urinalysis was within normal limits. Cerebral spinal fluid on admission showed an opening pressure of 190 mm. (water) and revealed 277 red blood cells, no white cells, 30 mg. % protein, 80 mg. % sugar (blood sugar, 120 mg. %), and a chloride level of 672 mg. %.

The patient continued to exhibit a spiking fever, with temperatures up to 105 F for three days and frequent episodes of nausea and vomiting. He became afebrile on the fourth hospital day. At this time it was noted that he had developed marked conjunctival injection and photophobia. At no time was icterus noted. A repeat lumbar puncture on the fourth hospital day revealed a clear fluid containing 10 white blood cells, 16 red cells, and normal sugar, protein, and chlorides. He still exhibited stiffness through the back, neck, and hamstrings but no muscle weakness. Hot packs and stretching were instituted because of a tentative diagnosis of nonparalytic poliomyelitis. This stiffness improved gradually, and at the time of discharge, on the eighth day, he was completely asymptomatic. No enteric virus was isolated from the stool, and serologic studies for the virus encephalitides were negative. However, the following serial serologic studies incriminated L. icterohaemorrhagiae as the etiologic agent.

	Day of Illness		
	1	12	34
L. icterohaemorrhagiae	Neg.	Pos. 1:256	Pos. 1:2,048
L. canicola	Neg.	Neg.	Neg.
L. pomona	Neg.	Neg.	Neg.

Comment.—The marked conjunctival injection in this patient was an important factor, leading us to consider the possibility of leptospirosis. However, only by a follow-up serologic study was the diagnosis established.

Case 5.—A 17-year-old white male student from Washington Court House, Ohio, was admitted to University Hospital on Aug. 3, 1956, with a history of abrupt onset of occipital headache accompanied by malaise, nausea, and vomiting seven days prior to admission. At that time he also noted muscle "ache" in his thighs and back. These symptoms subsided slowly, but on the day of admission he developed a severe frontal headache and stiffness of his neck. He was seen by his family physician, who performed a spinal fluid examination which revealed 591 white cells, of which 89% were lymphocytes. The headache and stiff neck were said to be moderately relieved by the lumbar puncture. He was then transferred to this hospital as a poliomyelitis suspect. On admission his temperature was 100.8 F. Ears, nose, and throat were not remarkable. Slight nuchal rigidity was noted, but no muscle weakness was detected. Deep-tendon reflexes were bilaterally hypoactive. No clinical or laboratory evidence of icterus was noted. Admission white blood cell count revealed 10,000 cells, of which 77% were neutrophils; 13%, lymphocytes; 5%, eosinophils, and 5%, monocytes. Urinalysis was unremarkable. Cerebral spinal fluid examination on admission revealed an opening pressure of 230 mm. (water) and 240 red and 389 white blood cells, of which 24% were neutrophils and 75% lymphocytes. Spinal fluid protein was 43 mg. %; sugar, 56 mg. % (blood sugar, 90 mg. %), and chlorides, 755 mg. %. Repeat examination of the spinal fluid on the third hospital day showed an opening pressure of 130 mm. and revealed clear fluid, with 19 red and 193 white blood cells, of which 88% were lymphocytes and 12% neutrophils. Spinal fluid protein was 22 mg. %; sugar, 58 mg. % (blood sugar, 103 mg. %), and chlorides, 755 mg. %. The fluid was negative for organisms on smear and culture. He rapidly improved, and he was asymptomatic when discharged after seven hospital days.

Studies for virus encephalitides were negative, but serologic studies for Leptospira were as follows:

	Day of Illness		
	10	14	25
L. icterohaemorrhagiae	Pos. 1:512	Pos. 1:512	Pos.1:512
L. canicola	Pos. 1:32	Pos. 1:16	Neg.
L. pomona	Neg.	Neg.	Neg.

Comment.—Although no rise in titer was observed, the initial and subsequent high titers, of 1:512, against L. icterohaemorrhagiae are strong evidence of leptospiral infection. He had had no illness in the previous two years which could even suggest previous infection. It is also of interest that this patient was from the same town as Case 3, above, who had entered this hospital exactly one month earlier.

CASE 6.—An 18-year-old white male hog farmer from New Holland, Ohio, was referred to University Hospital on July 22, 1957, as a possible case of poliomyelitis. Onset of illness was three days prior to admission, with symptoms of nausea and vomiting. On the morning of admission he noted onset of "dull" pain across his abdomen and low back as well as generalized weakness. He was seen by his family physician, who noted the presence of nuchal rigidity and a temperature of 102 F. He was then referred to the hospital. Past history was unremarkable, except for the fact that he had been swimming and water-skiing in local waters that summer, the last time on July 11, 1957.

On admission, physical examination revealed a temperature of 103.5 F, slight conjunctival injection, and moderate nuchal rigidity. In addition he had slight spasticity of his back muscles and complained of weakness of his trunk muscles. Neurologic examination failed to reveal any localizing signs. Admission white blood cell count was 9,200, with a normal differential. Urinalysis was within normal limits. Blood urea nitrogen was 20 mg. %. Total van den Bergh was 0.2 mg. %. Spinal fluid analysis revealed an opening pressure of 190 mm. (water) and clear fluid, with only 1 red and 1 white blood cell. Protein was 40 mg. %; sugar, 69 mg. % (blood sugar, 115 mg. %), and chloride, 695 mg. %.

The patient was treated supportively and became afebrile by the second hospital day. He was asymptomatic when discharged on the fifth day.

Again all virus studies were negative, but leptospiral agglutinations were as follows:

	Day of Illness	
	4	9
L. icterohaemorrhagiae	Neg.	Neg.
L. canicola	Neg.	Neg.
L. pomona	Pos. 1:128	Pos. 1:4,000

Comment.—The occurrence during the summer of an infection with predominant neurologic manifestations was considered as evidence for a tentative diagnosis of poliomyelitis. However, subsequent studies were compatible with an L. pomona infection. His occupational exposure to hogs correlated with this diagnosis.

CASE 7.—A 17-year-old white male student from New Holland, Ohio, was admitted on Aug. 6, 1957, with a chief complaint of severe headache, nausea, and vomiting of one week's duration. Actually, symptoms began 10 days before admission, at which time he noted the onset of persistent headache which gradually increased in severity over the following days. Seven days prior to admission he noted the onset of malaise and lethargy. Five days before admission he experienced nausea and vomiting and fever up to 104 F. On the day of admission he noted pain in his low back and slight stiffness of his neck. Also, at this time he had "sharp" frontal headache and felt dizzy. A friend with whom he had been camping was said to have had similar symptoms. There was no significant past history of any serious illness. Physical examination on admission revealed the patient to be afebrile but lethargic and drowsy. No jaundice was observed. Sclerae and conjunctivae were markedly injected. Pharynx was minimally injected. Slight nuchal rigidity was present. The remainder of the physical examination was within normal limits. White blood cell count on admission was 5,650, with an essentially normal differential. Urine was negative for protein, and red and white blood cells. Cerebral spinal fluid on admission showed an opening pressure of 210 mm. (water) and revealed 43 red blood cells and 350 white blood cells, of which 88% were lymphocytes and 12% neutrophils. Spinal fluid sugar was 64 mg. % (blood sugar, 115 mg. %); protein, 42 mg. %; chlorides, 695 mg. %. Also, it was negative for organisms on smear and culture.

The patient rapidly improved on supportive therapy and was discharged as well, on the seventh day, with a tentative diagnosis of virus encephalitis. All virus isolation and serologic studies were negative. However, serologic studies for Leptospira were as follows:

	Day of Illness	
	10	17
L. icterohaemorrhagiae	Neg.	Pos. 1:256
L. canicola	Doubtful pos.	Pos. 1:256
L. pomona	Doubtful pos.	Pos. 1:1,024

Comment.—Exposure to infected animals or their excreta while the patient was on

the camping trip most likely represents the source of the L. pomona infection. The patient's camping companion, although not examined, in all probability also represented a case of leptospirosis. It is of interest that this patient was from the same small town as Case 6, who also had L. pomona infection and was admitted to University Hospital two weeks previously.

CASE 8.—A 3-year-old white girl, from Nellie, Ohio, was admitted to University Hospital on May 27, 1956. Eight days prior to admission she developed a macular erythematous rash on her extremities and a fever of 104 F. One day prior to admission, lethargy, signs of meningeal irritation, and a petechial rash on her body were noted. On the day of admission, she had a generalized clonic seizure, which started in her left leg. On admission her blood pressure was 108/40. Her eyes exhibited a searching type of nystagmus and bilateral early papilledema. Her neck was supple. Skin examination revealed a generalized petechial rash, which was most marked on her extremities. She exhibited almost continuous clonic convulsions of her right arm, and shortly after admission she had a generalized clonic seizure. White blood cell count was 21,500. Urinalysis revealed 45 mg. % protein. Cerebral spinal fluid revealed 132 red and 8 white blood cells, with 75 mg. % sugar and 248 mg. % protein. Her temperature rose from 102 F to 106 F. The patient died shortly after admission, on her ninth day of illness. Blood cultures were all negative, and serologic tests for murine typhus, Rocky Mountain spotted fever, rickettsialpox, L. icterohaemorrhagiae, and L. pomona were all negative. Serologic test for L. canicola was positive at 1:512.

Postmortem examination revealed acute myocarditis, hemorrhagic pneumonia, and acute meningoencephalitis with subarachnoid hemorrhage. Special silver stains for Leptospira were said to be negative.

Comment.—The clinical course of this patient could be considered to be compatible with leptospirosis. The elevated serologic titer for L. canicola in a child who was said not to have been previously ill adds considerable weight to the diagnosis. The failure to find Leptospira in silver stains of the tissues is not significant, since in a previous report[15] of 13 fatal cases of leptospirosis the organism was not demonstrated in 4 cases.

CASE 9.—A 28-year-old Negro woman from Columbus was admitted to University Hospital on Sept. 19, 1958, as a poliomyelitis suspect. Three days before admission she noted fever, malaise, and leg pain. The next day she experienced weakness in her legs. On the day before admission her leg pain became increasingly severe, and she had severe constant headache. In addition there was pain in her left forearm and increasing fever up to 104 F.

Physical examination on admission revealed an acutely ill patient exhibiting a temperature of 104 F. Other positive findings included marked nuchal rigidity, moderate pharyngeal injection, and generalized muscle tenderness but no weakness. White blood cell count was 7,200, with 83% neutrophils and 17% lymphocytes. Cerebral spinal fluid on admission showed 195 red blood cells and no white cells; protein was 15 mg. %; chlorides, 712 mg. %, and sugar, 50 mg. % (blood sugar, 106 mg. %). With the negative spinal fluid findings, the patient was treated with penicillin as a possible streptococcal pharyngitis, and her temperature gradually returned to normal by the fourth hospital day. However, in view of the fact that her headache and nuchal rigidity persisted, another lumbar puncture was performed at this time. The fluid revealed an opening pressure of 150 mm. (water) and closing pressure of 80 mm. At this time the fluid contained 203 white blood cells, of which 96% were lymphocytes and 30 red blood cells; protein was 36 mg. %; chlorides, 750 mg. %, and sugar, 46 mg. % (blood sugar, 132 mg. %). Her headache and nuchal rigidity disappeared after this procedure.

On the sixth hospital day another lumbar puncture revealed 147 white blood cells, of which 96% were lymphocytes; protein was 18 mg. %; chlorides, 731 mg. %; sugar, 66 mg. % (blood sugar, 110 mg. %). The patient was discharged on the 10th hospital day with a tentative diagnosis of aseptic meningitis. All virus studies were negative, but leptospiral agglutinations were as follows:

	Day of Illness	
	4	10
L. icterohaemorrhagiae	Neg.	Pos. 1:2,048
L. canicola	Neg.	Pos. 1:2,048
L. pomona	Neg.	Pos. 1:64

Comment.—Although the initial spinal fluid examination was negative, repeat studies on two occasions showed a pleocytosis. The second spinal fluid sugar was slightly depressed, and this led us to consider tuberculous meningitis in the differential diagnosis. However, the repeat examination several days later showed a normal sugar content. This patient lived in an area of Columbus where exposure to Leptospira is not unlikely.

CASE 10.—A 12-year-old white farm girl from Bellefontaine, Ohio, was admitted to University Hospital on Sept. 28, 1958. Her chief complaint was headache and backache of one week's duration, associated with chills, fever, and nausea.

Physical examination revealed a patient in no acute distress. Temperature was 101.6 F. Other physical findings were negative except for moderate nuchal rigidity. Blood cell count on admission revealed 10,500 white blood cells, of which 68% were neutrophils. Lumbar puncture showed an opening pressure of 210 mm. (water) and closing pressure of 150 mm. There were 49 red blood cells and 474 white cells, with 88% lymphocytes; protein was 46 mg. %; chlorides, 690 mg. %, and sugar, 47 mg. % (blood sugar, 103 mg. %). The patient continued to have a fever (temperature up to 101.5 F) for three days and then became afebrile and asymptomatic. In view of the slightly depressed spinal fluid sugar, lumbar puncture was repeated on the third hospital day. At this time there were 10 red blood cells and 224 white blood cells, of which 97% were lymphocytes; protein was 50 mg. %; chlorides, 716 mg. %, and the sugar was again slightly depressed, with 48 mg. % (blood sugar, 105 mg. %). Although the patient was asymptomatic, the possibility of tuberculous meningitis was being considered. Therefore, another spinal fluid examination was performed on the fifth hospital day. At this time 5 red blood cells and 1,005 white blood cells, all lymphocytes, were noted; protein was 59 mg. %; chlorides, 724 mg. %, and sugar, even more depressed, with 39 mg. % (blood sugar, 108 mg. %). The patient was then placed on antituberculous therapy as a precautionary measure. After one week of therapy another lumbar puncture was performed. At this time there were 22 red blood cells and 253 white blood cells, of which 99% were lymphocytes. Protein was 36 mg. %; chlorides, 745 mg. %, and sugar, 46 mg. % (blood sugar, 87 mg. %). In view of the return of spinal fluid sugar to normal and the negative tuberculin test, it was felt that this patient did not have tuberculous meningitis. However, she was continued on therapy pending the next lumbar puncture performed one week later, on Oct. 10. At this time her fluid revealed 93 white blood cells, of which 99% were lymphocytes; proteins were 24 mg. %; chlorides, 711 mg. %, and sugar, 56 mg. % (blood sugar, 104 mg. %).

The patient was then discharged on no therapy on the twenty-fourth hospital day. Studies for virus etiology were negative, but the Leptospira agglutination tests were as follows:

	Day of Illness			
	10	12	23	30
L. icterohaemorrhagiae	Neg.	Neg.	Pos. 1:32	Pos. 1:128
L. canicola	Neg.	Neg.	Neg.	Neg.
L. pomona	Pos. 1:64	Pos. 1:128	Pos. 1:2,048	Pos. 1:4,096

Comment.—This patient represented an instance of chronic meningitis due to L. pomona. She had had considerable exposure to farm animals at home. The temporary depression of spinal fluid sugar led us to consider tuberculous meningitis strongly enough to institute therapy.

Comment

The ideal method of proving the specific etiology of leptospirosis is the isolation of the organism. This procedure is not routine in most general hospitals. The more convenient and indirect method of serologic diagnosis can be delegated more readily to special laboratories performing these services. However, unless the possibility of leptospiral infection is suspected and studies are requested in that direction, leptospirosis can readily escape detection. It has been our practice to include leptospiral studies in our approach in the differential diagnosis of the aseptic meningitides. The patients reported here all had negative findings by virus isolation and viral serologic methods. In 8 of the 10 patients highly significant titer rises occurred to incriminate a leptospiral agent. Since cross reactions do occur, one cannot always state specifically which Leptospira was the offending agent. However, in Patients 1, 2, and 4 infection was most likely due to L. icterohaemorrhagiae; these three patients were from the greater Columbus area. Patient 3, from Washington Court House, Ohio, had the same titers for both L. icterohaemorrhagiae and L. pomona and could have been infected by either strain. Similarly, Patient 9, from Columbus, had the same titer for both L. icterohaemorrhagiae and L. canicola. On the other hand, apparent L. pomona infection was observed in both Patients 6 and 7, who entered the hospital within two weeks of each other from the same small community of New Holland, Ohio, and in Patient 10, who lived

on a farm in Bellefontaine, Ohio. Patient 5, who exhibited an initial titer of 1:512 against L. icterohaemorrhagiae, showed no change in titer two weeks later. Thus, the failure to show a rise might be against the diagnosis of leptospirosis, and this could represent previous infection. However, this titer is certainly higher than one observes ordinarily, and the absence of any other illness during the past several years suggests that this patient could have had leptospiral meningitis. Patient 8, in her brief one-day hospital stay, represented a diagnostic problem. The clinical course and L. canicola titer of 1:512 suggest the possibility of a leptospiral etiology.

In recent years there has been an increase in reported cases of leptospirosis in the United States. From 1905 to 1948, there were 299 cases reported.[16] From 1951 to 1956, a total of 488 cases were reported.[2] Improved diagnostic procedures and greater awareness of this disease must account for a considerable proportion of the increased incidence, as demonstrated in our own observations at University Hospital. It is also of interest that the peak incidence of cases in the United States occurs during the summer and early fall months. Eight of our ten patients were admitted between July and September.

The failure of recognition of leptospirosis as such must obviously play an important role in the relative sparseness of reports of cases of this type of infection in this country. The wide variety of clinical signs and symptoms presented by this disease certainly adds to the problem. Leptospirosis, however, can be conveniently divided into icteric and anicteric forms.

The icteric type apparently presents less of a problem in diagnosis, in that jaundice may eventually lead one to think of leptospirosis. This is indicated by the report of Molner, Myer, and Raskin,[16] where 78 cases which occurred in the Detroit area were not diagnosed until the second, or the icteric, stage of the disease had been reached. Although many manifestations of the disease other than jaundice are common to both forms, it is the anicteric type which appears to be the more difficult to diagnose. Thus, the failure to appreciate the fact that nonicteric leptospirosis does occur decreases the incidence of recognition.

Since leptospirosis is usually a generalized systemic infection, one should expect to find protean signs and symptoms.[3] It is the purpose of this paper to stress the manifestations of central nervous system involvement. In the present series of 10 cases, all presented themselves with central nervous system manifestations, which varied from mild meningeal irritation to coma. Whenever we encounter a patient with such presenting signs, we consider leptospirosis in our differential diagnosis.

Cerebral spinal fluid findings in leptospirosis unfortunately are not diagnostic. In our patients these findings varied from a normal fluid early in the course of the disease to mild pleocytosis and a mild increase in protein later. Sugar and chloride levels usually remained within normal limits, although there was a temporary depression of spinal fluid sugar in Patients 2, 9, and 10. These findings plus the clinical picture of meningeal irritation lead one to consider a viral infection of the central nervous system, such as viral encephalitis or poliomyelitis, or tuberculous meningitis when the sugar is depressed. For example, Ramsay [12] reported a case of canicola fever with neurologic complications simulating cervical radiculitis. He also referred to four cases of canicola fever which closely simulated poliomyelitis. Our one fatality may have been due to L. canicola. Two deaths due to L. canicola infections have been reported,[17,18] both of which were said to have been the result of renal involvement.

Examination of the formed elements of the blood aids little in the diagnosis of leptospirosis, since there may be no change in the white cell count or a moderate leukocytosis. The main clinical characteristics of leptospirosis appear to be the sudden onset of the illness, severe myalgia, mainly

of the leg muscles, conjunctival injection, and fever. Lack of any localizing neurologic signs also may aid in the diagnosis. Macular or maculopapular eruption, as observed in Case 8, is not uncommon.[3] The rash at times may assume a petechial character.

Correct diagnosis of leptospirosis relies to a great extent on leptospiral agglutination tests. Evaluation of serial blood samples with a rising titer is the best evidence for present infection. One would expect to see a rise in titer at approximately 12 days, although it may rise as early as 6 to 7 days. Maximum titers are generally observed in the second or third week of the disease. The titers may remain elevated above normal for up to one year.[19]

It has been suggested that penicillin, streptomycin, chlortetracycline, and oxytetracycline are useful in the treatment of early L. icterohaemorrhagiae or L. canicola infections in guinea pigs, hamsters, or mice.[20] In contrast, these therapeutic agents had little to offer once the disease was well advanced clinically. The treatment of leptospirosis leaves much to be desired. A very limited number of cases appear to have improved to some extent after treatment with penicillin, chlortetracycline, or oxytetracycline.[21-23] However, the vast majority of cases received no therapy or were not benefited by the therapy administered. This discrepancy between human and animal response to drugs most likely is due to the fact that few clinical cases of leptospirosis are diagnosed early. Thus, it seems proper to conclude that if any advancement in the clinical management of this disease is to be made, early and accurate diagnosis must be accomplished.

Summary

Ten cases of leptospirosis with predominantly neurologic manifestations are presented. The similarity of leptospiral meningitis to other infections of the central nervous system, such as viral encephalitis and poliomyelitis, has been pointed out. Accurate diagnosis of leptospirosis to a great extent depends upon (*a*) recognition of the protean nature of infections with Leptospira, (*b*) realization of the fact that leptospirosis is in all probability more prevalent in the United States than is usually accepted, and (*c*) adequate laboratory facilities for serologic determinations.

Serologic agglutination tests were performed by the Division of Laboratories of the Ohio Department of Health, Columbus.

The Ohio State University, The Health Center (10).

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Preparation of Leptospiral Antigens and Techniques for Performance of the Agglutination Tests *

1. Antigen strains of leptospirae are grown in a modified (Schuffner's) medium (Verwoort's liquid).

2. Medium for antigen preparation is distributed in 100 ml. amounts in 250 ml. Erlenmeyer flasks. Antigens are grown in prescription bottles. Seed and stock cultures are grown in screw-cap test tubes.

3. Seed cultures are grown in 10 ml. amounts in 50 ml. capacity Erlenmeyer flasks. Stock strains are maintained at 25 C in a volume of 3 ml. in 16×125 mm. screw-cap tubes (to prevent evaporation). Stock strains are transferred every four weeks.

4. Inocula: For 100 ml. of antigen approximately 10 ml. of culture is used (the contents of one seed flask) to inoculate the antigen flask. In preparing seed cultures, 1.0 ml. of culture is used to inoculate each seed flask containing 10 ml. of media.

These inocula are heavy but give better and more consistent growth results than lighter ones.

5. Antigens are incubated at 27 C ±1 (B. O. D. incubator) for three to five days. Maximum or sufficient growth has usually occurred at the end of the fifth day of the incubation period.

6. After incubation, antigen cultures are examined for purity (dark field and stained smear to detect bacterial contaminants) and for density (dark field, ×100). There is no very good and convenient method, at present, for standardizing density of antigens. Preparations are considered to be of satisfactory density when a loopful of culture, viewed under low power of the dark-field microscope, shows little free space between individual organisms. (Density and certain other factors undoubtedly affect sensitivity of antigens.)

7. After sufficient growth has occurred, the culture is formulated with Reagent Formaldehyde Merck Neutral 36%-38% HCHO to a final concentration of 0.3%. Since the pH of all so-called "neutral" formaldehyde preparations is not always 7.0, the pH of the antigen, after addition of formalin, should be checked and readjusted if necessary to pH 7.2-7.4. Phenol red indicator (0.2 gm. phenolsulfonphthalein powder in 100 ml. of 80% ethyl alcohol) may be added directly to the antigen preparations to guide pH adjustments, if used in minimum amounts to give color to fluid. Allow formalized antigens to stand at room temperature for 24 hours.

8. Centrifuge the antigens lightly (500-1,000 rpm) for 5-10 minutes to remove precipitate and debris. Decant supernatant into sterile tubes or bottles. This is the antigen to be used in testing. Store at room temperature. Antigens should be checked before each use by dark-field examination (×100) for tendency toward autoagglutination. Any rough or autoagglutinated antigens must be discarded.

Preparation of Leptospiral Antigens.—Before use, each new batch of antigen must be titrated for sensitivity. Variations in sensitivity of different batches of antigens may be detected and more or less controlled, until better methods are available, by titrating each batch of antigen against a known positive rabbit antiserum. Antigens showing variation in titer of more than two or three tubes, in a twofold falling dilution series, from previous titrations of the control serum should not be used in diagnostic tests, in our opinion.

A further check is always made in this laboratory by freezing at —5 C all first serum specimens received from a particular patient and rerunning each such specimen with the second specimen on the same patient, when it is received.

* From Ohio Department of Health, Columbus.

If antigen preparations are to be kept more than two weeks, they should be retitrated for sensitivity at the end of two weeks, whether they appear autoagglutinated or not.

The Agglutination Test

1. Multiple series of twofold falling dilutions of the unknown serum are made in final volume of 0.2 ml. (The number of sets of dilutions is determined by the number of antigens to be used, i. e., one set of dilutions for each antigen.)

First Tube: 0.1 ml. of unknown serum +0.3 ml. of normal saline. Mix thoroughly with pipette.

Second Tube: 0.2 ml. of diluted serum from first +0.2 ml. of saline, and so on, through series.

We use 1 ml. pipettes for measuring serum to go into first tube, then Cornwall pipetting units, set to deliver 0.2 ml., for subsequent dilutions. Discard 0.2 ml. of diluted serum from last tube. Rinse pipetting unit thoroughly with saline before using for second set of dilutions.

Since "prozone" phenomena rarely, if ever, occur in even high-titer Leptospira sera, a preliminary screening set of five (we screen at two dilutions, 1:50 and 1:100) dilutions is used for each unknown. Sera positive in the last tube of the screening set are retitrated in 15-20 tubes subsequently (or to titer).

In a reference diagnosis service, where no more than 10%-20% of the sera are positive, we feel that this preliminary screening in relatively few tubes represents a definite saving in time and materials.

For purposes of conservation of antigen, where a large number of specimens are to be examined, we prefer to use the smallest possible volume; 0.2 ml. of serum +0.2 ml. of antigen is satisfactory.

Preparation of Leptospiral Antigens.—1. Although some workers use 1:50, 1:100, etc. dilutions for screening purposes, we prefer the above procedure, since it eliminates the transfer (and possible error) of diluted serum to the serological tubes for testing.

2. To each tube of one series of diluted serum, 0.2 ml. of Leptospira icterohaemorrhagiae antigen is added; similarly to the second series, Leptospira canicola is added, and to the third Leptospira pomona antigen, etc.

3. The following controls are used with each set of tests: Positive: 0.2 ml. of known specific antiserum +0.2 ml. of homologous antigen (one positive for each species of Leptospira used): Negative: 0.2 ml. of saline or known negative serum +0.2 ml. of antigen (one negative for each species).

4. After the addition of antigens, the rack of tubes is thoroughly shaken and incubated in a 45-50 C water bath for two hours.

5. Refrigerate tubes for one hour before reading. This procedure makes end-points somewhat easier to determine than if results are read immediately.

6. To read the test, a generous loopful of material from each tube (shake tube before withdrawing fluid) is placed on a clean slide. (Slides are kept in alcohol and dried with soft towel as needed.) Each drop is examined under low-power dark field (× 100) for evidence of agglutinations. Titer is reported as the highest serum dilution giving definite agglutinations.

Notes

1. In preparing slides for reading, 5 drops (i. e., fluid from five different tubes) may conveniently be placed on a single slide. After some practice, the worker will be able to read all five before the drops begin to dry up.

2. If, in preparing the slides for reading the tests, one starts taking fluid from the tube containing the highest dilution of serum (i. e., from fifth tube in screening), the loop need not be flamed between tubes so long as formalized antigens are used. Fluid remaining in the loop may be knocked off by tapping against the desk. Of course flaming of the loop is essential in going from a positive to negative control tube.

Leptospiral Meningitis

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Although research on the leptospiroses was initiated in 1886 with Weil's report on the clinical picture of a disease suspected to be a separate entity, it was not until 1910 that the first cases of what appeared to be meningitis of leptospiral origin were reported in the French medical literature.[1-4] In 1915, Inada and Ido, in Japan, and Uhlenhuth and Fromme, in Germany, proved that Weil's disease was caused by a spirochete, which was later classified as Leptospira by Noguchi.[1,2,5] Conclusive experimental evidence in support of the role of the Leptospira icterohaemorrhagiae in the production of meningeal manifestations, which frequently accompany the leptospiroses in the icteric and anicteric forms, appeared in 1916.[6,7] Physical signs and symptoms of meningitis have been reported in 10% to 33% of large series of cases in the European medical literature.[8,9] However, even in the absence of clinical signs pointing to meningeal involvement, significant alterations of the spinal fluid in both the icteric and the anicteric are observed in 30% to 100% of the cases.[10-17]

The first mention of the possibility of the existence of leptospirosis in Puerto Rico was made in 1918.[18] This observation was made scarcely two years after the discovery of the pathogenic leptospirae in Japan and Germany. The isolation and identification of L. icterohaemorrhagiae in patients, as well as in rats and wild mice, was made in 1940.[20] In 1941, positive serological reactions from jaundiced patients known to have acquired the disease in Puerto Rico were reported.[21] These investigations led to an increasing interest in the disease, and by 1948, several cases had been reported, including an infection with Leptospira canicola, on the basis of serological tests.[22,23]

A total of 235 cases have been discovered between 1948 and 1956; several papers based on the study of 208 cases have been published,[24-28] and thorough clinical, laboratory, and epidemiological analyses are now ready for press.

In this paper we will attempt to present the most salient clinical features of the disease, with special emphasis on the meningeal aspects.

Material and Methods

Of the 235 cases studied, 40 were subjected to one or more lumbar taps. Twenty-one (52%) of these patients showed signs of central nervous system involvement, consisting of mild or severe meningeal irritation, delirium, convulsions, and coma. The other 19 patients were free of signs and symptoms of meningitis, and the procedure was intended for routine laboratory studies in an attempt to isolate and classify the leptospirae from the spinal fluid. The latter group was selected at random, and it included 12 anicteric and 7 icteric patients.

The criteria for diagnosis consisted of one or more of the following: (1) isolation and identification of the leptospirae in the blood, spinal fluid, and/or urine; (2) serological evidence of infection (complement-fixation and agglutination-lysis test) consistent with the clinical picture of the disease, and (3) postmortem evidence of classical Weil's disease.

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Results

Clinical Features

There were 29 males and 11 females, with ages ranging from 7 to 58 years, and 32 were younger than 40 years. All the patients were indigents of the San Juan metropolitan area; most were unskilled laborers, and all lived in areas where rats abounded and where water pollution by the excrements of these rodents was possible.

The incubation period varied from 7 to 14 days. The onset was acute and explosive, and the disease was ushered in by chills of variable intensity, a rapidly rising fever with prostration, severe general malaise, intense headache, and muscle aches and pains. Nausea and vomiting were recorded in most instances. Burning of the eyes, with photophobia and slight lacrimation, was a predominant symptom. A variable limitation of urinary output was frequently observed from early in the course of the disease.

Bulbar and palpebral conjunctivitis, one of the most significant physical signs of leptospirosis, was present in all cases. Conjunctival hemorrhages were observed in two icteric patients. The conjunctival alterations generally appeared within the first week of the disease and persisted for an average of seven days. Moderate to severe myalgia appeared at onset and persisted until deferverscence in 38 of the 40 cases studied for meningeal alterations. It was most distressing when the large muscular masses of the back, thighs, calves, deltoids, and neck were squeezed or tapped. Most patients lay on their backs and were disturbed by any kind of movement. Muscle pains and tenderness could not be elicited in the two comatose patients. It must be emphasized at this juncture that the intensity of myalgia bore no relation to the presence of jaundice or to the signs of meningeal irritation. No difference in the intensity and quality of the cephalalgia could be discerned in those with, or without, meningeal involvement.

Pharyngitis was frequently observed, but its pathogenesis remains unexplained. However, it was noted more frequently among those who had nausea and vomiting, which was present in 22 instances. Hematemesis, leading to shock and death on the eighth day of illness, was observed once. Cough with scanty expectoration was recorded in 12 cases. The sputum was blood tinged in two instances. Crepitant rales were heard in seven icteric and two anicteric cases, and a radiological diagnosis of patchy pneumonitis was reported in two icteric and one anicteric patients.

Diarrhea was observed at onset in five cases. It lasted for two to eight days. Mild to moderate hepatic enlargement was recorded in 29 instances. This was as common in the icteric as in the anicteric. The tip of the spleen was palpated in an anicteric case (Table 1).

TABLE 1.—*Clinical Findings in Forty Cases of Leptospirosis*

	Central Nervous System Manifestations		
	With	Without	Total
Cases, no.	21	19	40
Sudden onset	21	19	40
Fever	21	19	40
Headache	21	19	40
Conjuctivitis	21	19	40
Muscle tenderness	19 (2 were comatose)	19	38 (2 were comatose)
Hepatomegaly	18	11	29
Vomiting	12	10	22
Jaundice	13	7	20
Skin rash	10	8	18
Hypotension	6	6	12
Rales	7	3	10
Diarrhea	2	3	5
Admitted before 5th day	11	17	28

Jaundice appeared during the first week of illness among the 20 cases of classical Weil's disease studied, with maximum serum bilirubin values of 2 to 41 mg. (average 18 mg. per 100 cc. of blood), and it subsided within 4 to 50 days. It must be emphasized that five of the seven patients with persistent icterus for over 26 days developed symptoms and signs pointing to disturbances in the central nervous system.

Leukocytosis was a prominent feature in 18 cases, with counts as high as 46,800

TABLE 2.—*Laboratory Findings in Forty Cases of Leptospirosis*

	Central Nervous System Manifestations						
	With		Without		Total		Total, %
	Present	Absent	Present	Absent	Present	Absent	
Anemia	2	19	2	17	4	36	10
Leukocytosis	9	12	8	11	18	22	45
Azotemia	12	5	6	10	18	15	55
Albuminuria	14	7	13	6	27	13	68
Pyuria	3	18	2	17	5	35	12.5
Hematuria	1	20	2	17	3	37	7.5
Abnormal cephalin flocculation test	7	0	8	3	16	3	84
Abnormal thymol turbidity test	5	9	2	15	7	24	23
Hyperglobulinemia	4	1	1	1	5	2	72
Hypoprothrombinemia	2	4	0	6	2	10	17

per cubic millimeter of blood in a deeply jaundiced patient. Since significant leukocytosis is encountered in no more than 70% of the icteric and 60% of the anicteric forms of leptospirosis and leukopenia is not a rarity in both forms of leptospirosis, it must be concluded that it does not bear any relation to the meningeal manifestations. Petechiae and ecchymosis were encountered in 11 icteric and 2 anicteric patients.

Variable degrees of albuminuria were discovered in 27 cases; microscopic hematuria, in 3, and pyuria, in 6. Azotemia was evident in 18 of the 33 cases tested (Table 2). The highest values of blood nonprotein nitrogen were found among the icteric cases, with maximum levels of 210 and 214 mg. per 100 cc. in two instances. The latter suffered from involvement of the central nervous system, with one death. The highest value of blood nonprotein nitrogen among the anicteric was 80 mg. per 100 cc., with no deaths. The data would tend to suggest that the anicteric form of leptospirosis is seldom accompanied by serious renal or hepatic disturbances and that, although the clinical course is abbreviated as compared with classical Weil's disease, the extreme severity of the symptoms at onset render its prognosis unpredictable. On the other hand, there was a significant correlation between the severity of the involvement of the central nervous manifestations and the renal and hepatic alterations. Thus, three of the deeply icteric patients presenting alterations of the central nervous system died. In two, death was attributed to renal failure, with blood nonprotein nitrogen values of 214 and 103 mg. per 100 cc. on the 11th and 18th days of illness, respectively, and the other, to severe upper gastrointestinal bleeding, with irreversible shock on the 8th day. It must also be emphasized that three of the four comatose patients died (Table 3).

Circulating leptospiral antibodies usually appeared within 6 to 12 days of illness. Positive agglutination tests for L. icterohaemorrhagiae were encountered by the end of the second week in every instance. The leptospirae were isolated from the blood in 25 of the 40 cases studied.

The condition was unresponsive to therapeutic doses of sulfadiazine, penicillin, oxytetracycline, streptomycin, and chloramphenicol. The fever usually subsided by

TABLE 3.—*Central Nervous System Manifestations*

	Meningeal Irritation	Convulsions	Lethargy & Stupor	Incoherence & Delirium	Coma	Death
Icteric cases (13)	10	1	6	3	4	3
Anicteric cases (8)	8	0	3	1	0	0

TABLE 4.—*Spinal Fluid Findings in Icteric Cases with Central Nervous System Manifestations*

Case No.	Day of Disease	Fluid Color	Total Cells	P. M. N., %	Lympho-cytes, %	Proteins	Sugar	Chlorides	Leptospirae	Comments
1	10	Clear	228	19	81	60	43	600	--	Died on 11th day
2	8	Yellow	195	10	90	136	52	--	No	
3	4	Clear	166	0	100	98	65	--	No	
4	5	Clear	57	15	85	--	66	628	No	
5	6	Clear	57	15	85	--	--	--	Yes	
6	6	Clear	32	0	100	15	--	--	--	
7	14	Yellow	22	50	50	10	76	710	--	
8	13	Clear	10	20	80	40	62	--	No	Died on 18th day
9	7	Yellow	7	0	100	78	--	--	Yes	Died on 8th day
10	5	Clear	4	0	100	20	73	--	--	
11	9	Clear	3	0	100	50	62	--	No	
12	6	Yellow	2	0	100	40	--	--	Yes	Coma
13	5	Clear	--	--	--	--	--	--	Yes	

lysis, with a concomitant disappearance of headache, myalgia, and conjunctivitis in all the anicteric and in the nonfatal icteric cases. There was a rapid decrease in the blood nonprotein and urea nitrogen and a slower decrease in the levels of serum bilirubin in the cases of classical Weil's disease. As emphasized previously, the clinical course was shorter in the anicteric group of cases. It has been stated that all the patients suffered from headache and that 21 of these presented other phenomena pointing to a pathological disturbance of the central nervous system. Of the latter, 13 were icteric, and of these 10 showed signs of meningeal irritation on admission, as evidenced by stiffness of the neck and/or a positive Kernig's test. Lethargy and stupor were predominant symptoms in six instances, and three became progressively incoherent, delirious, and comatose, with two deaths. Generalized convulsions were observed in a 52-year-old woman, admitted in a comatose state on the 10th day of illness. She died within the first 24 hours after hospitalization. Since all the reported fatalities presented serious renal and hepatic involvement, the role played by a leptospiral invasion of the central nervous system as a dominant or as a secondary mechanism of death remains unassessed.

Spinal Fluid in Icteric Patients with Central Nervous System Manifestations

For the sake of clarity the spinal fluid findings in the icteric cases presenting central nervous system manifestations are summarized in Table 4. It was interesting to observe that the fluid was icteric in four cases, with serum bilirubin levels (determined on the same day of the lumbar tap) of 8.6 to 24 mg. per 100 cc. of blood in three and an icterus index of 186 in another. It seems paradoxical that serum bilirubin values of 16.8 to 29.4 mg. per 100 cc. of blood were discovered in five and an icterus index of 124 in another and that none of these showed icteric spinal fluids (Table 5). This observation seems to minimize the

TABLE 5.—*Correlation of Icteric Index and Serum Bilirubin with Appearance of Spinal Fluid* *

Case No.	Appearance of Fluid	Serum Bilirubin, Mg/100 Cc.		Icteric Index
		Direct	Total	
1	Icteric	--	--	186
2	Icteric	4.8	8.6	
3	Icteric	5.9	15.8	
4	Icteric	13	24	
5	Clear	12	29.4	
6	Clear	14	26	
7	Clear	--	--	124
8	Clear	15	23	
9	Clear	10.9	16.8	

* Nine cases in which procedures done on same day.

value of the alterations in color of the spinal fluid as a diagnostic sign in classical Weil's disease.

Pleocytosis, ranging from 10 to 228 white blood cells per cubic millimeter of spinal fluid, with 50% to 100% lymphocytes, was encountered in eight instances. Abnormal values of proteins, with a maximum level of 136 mg. %, were recorded in four cases. One of the latter showed an icteric-tinged fluid without pleocytosis. The glucose content was significantly altered in a fatal case; that of chlorides (measured as sodium chloride), in a patient who recovered. L. icterohaemorrhagiae was isolated from the spinal fluid in four of the icteric cases presenting meningeal manifestations during the first week of illness.

Case of Classical Weil's Disease with Central Nervous System Manifestations

A 38-year-old, chronic alcoholic, Puerto Rican carpenter was suddenly taken with general malaise, anorexia, weakness, chills, fever, headache, and severe pains in the lower extremities, which forced him to take to bed. He rapidly became delirious and incoherent, and jaundice appeared within the first three days of illness. Examination on the seventh day of illness revealed an undernourished, incoherent, markedly dehydrated, and deeply jaundiced patient, with a temperature of 100.2 F, pulse of 90 and respirations of 24 per minute, and a blood pressure of 70/30 mm. Hg. The conjunctivae were intensely injected. Several petechiae were observed over the lateral aspects of the chest. A tender liver was palpated 5 cm. below the right costal border in the right midclavicular line. Moderate muscular tenderness was elicited on squeezing or tapping the muscles of the lower extremities and back.

The hemoglobin values ranged from 9 to 10.5 gm. per 100 cc.; the erythrocyte count, from 2,680,000 to 2,830,000 per cubic millimeter of blood, and the leukocyte count, from 5,300 to 24,000, with a significant neutrophylic leukocytosis. The highest blood nonprotein nitrogen was 142 mg., and the serum bilirubin, 36 mg. per 100 cc. (Chart 1). Urinalyses revealed transitory pyuria, mild albuminuria, and cylindruria, as well as bile pigments and an increased urobilinogen. The total serum proteins were 6.8 gm. per 100 cc., with 4 gm. of globulins. The cephalin flocculation was 4+ in 24 hours. The prothrombin time and thymol turbidity were normal. Ova of Schistosoma mansoni and Necator americanus were present in the stools. The serologic test for syphilis was negative. The chest x-rays revealed a linear pneumonitis in the right lower lung. The spinal fluid was pale yellow and contained 195 cells per cubic millimeter, with 90% lymphocytes, 126 mg. of protein, 82 mg. of glucose, and a total bilirubin of 1.25 mg. % on the eighth day of illness. Although the complement-fixation test for leptospirosis was doubtful on the eighth, positive and increasing values appeared after the ninth day of illness.

Though he received intravenous dextrose in water, penicillin, and streptomycin, he remained febrile, incoherent, and delirious. The urine output ranged from 1,200 to 1,300 cc. On the ninth day, he suddenly developed dyspnea, cyanosis, and wheezing respirations, which were relieved by the intravenous administration of aminophylline. The urinary output increased to over 2,000 cc. per day on the 12th day of illness, and this was followed by decreasing azotemia and a gradual improvement of the mental status. By the 24th day he was mentally alert and the liver had decreased in size

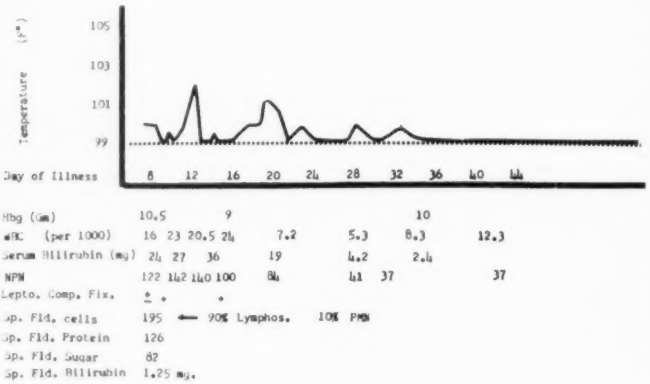
Temperature (F.)
105
103
101
99
Day of Illness
8 12 16 20 24 28 32 36 40 44
Hbg (Gm) 10.5 9 10
WBC (per 1000) 16 23 20.5 24 7.2 5.3 8.3 12.3
Serum Bilirubin (mg) 24 27 36 19 4.2 2.4
NPN 122 142 140 100 84 41 37 37
Lepto. Comp. Fix. ± + +
Sp. Fld. cells 195 ← 90% Lymphos. 10% PMN
Sp. Fld. Protein 126
Sp. Fld. Sugar 82
Sp. Fld. Bilirubin 1.25 mg.

Chart 1.—A case of classical Weil's disease with meningitis.

TABLE 6.—*Spinal Fluid Findings in Anicteric Cases with Central Nervous System Manifestations*

Case No.	Day of Disease	Color of Fluid	Total Cells	P. M. N., %	Lymphocytes, %	Proteins	Sugar	Chlorides	Leptospirae
14	7	Clear	440	6	94	90	68	...	...
	9	Clear	110	30	70	45	66	725	...
	20	Clear	26	36	64	65	68	...	...
15	5	Clear	429	60	40	120	63	...	...
16	7	Clear	166	70	30	60	62	...	...
17	5	Clear	0	0	0	...	...	...	No
	7	Clear	115	64	36	40	80	660	Yes
	8	Clear	88	60	40	40	110	693	No
18	10	Clear	9	0	100	...	...	...	...
19	5	Clear	0	0	0	31	62	726	...
20	5	Clear	2	0	100	22	...	660	Yes
21	3	Clear	0	0	0	28	100	685	No

to 3 cm. below the costal border. The fever disappeared on the 32d and jaundice on the 40th day of illness.

Comment.—This exemplifies a case of classical Weil's disease with signs of intense nervous system manifestations. Whether the latter were mainly governed by the direct effect of the leptospirae on the meninges and brain remains unanswered. However, there were signs of intense toxemia, as evidenced by the persistent fever, intense jaundice, and severe azotemia, which perhaps dominated the clinical picture of the disease.

Spinal Fluid in Anicteric Patients with Signs of Central Nervous System Manifestations

The spinal fluid was studied in eight anicteric cases with meningeal irritation (Table 6). Pleocytosis of 26 to 440 white blood cells per cubic millimeter of spinal fluid, with 36% to 94% lymphocytes, was encountered in four instances; increased proteins, in three, and slightly decreased chlorides, in one. L. icterohaemorrhagiae was isolated in three of the five cases tested. The etiologic agent was recovered once from a spinal fluid with slightly decreased chlorides, but this was otherwise normal.

Spinal Fluid in Classical Weil's Disease Without Signs of Central Nervous System Manifestations

The findings of seven cases of classical Weil's disease without clinically detectable central nervous system involvement are summarized in Table 7. It was noted that there were no changes in the color of the fluid, even when the L. icterohaemorrhagiae were isolated from samples in three of the five cases tested during the first week of illness. A definite pleocytosis was encountered in three, with increased proteins in two instances. The lack of correlation of pigmentations of the spinal fluid in the presence of high serum bilirubin values is reemphasized.

Spinal Fluid in Anicteric Leptospirosis Without Central Nervous System Manifestations

Of the 12 anicteric cases without central nervous system manifestations, studied in

TABLE 7.—*Spinal Fluid Findings in Icteric Cases Without Central Nervous System Manifestations*

Case No.	Day of Disease	Color of Fluid	Total Cells	P. M. N., %	Lymphocytes, %	Proteins	Sugar	Chlorides	Leptospirae
22	7	Clear	33	...	...	68	78	...	Yes
23	6	Clear	13	0	100	30	66	...	No
24	7	Clear	9	11	89	72	70	...	...
25	7	Clear	3	0	100	37	58	...	...
26	3	Clear	0	0	0	17	68	...	No
27	7	Clear	0	0	0	25	120	...	Yes
28	3	Clear	0	0	0	...	...	...	Yes

TABLE 8.—*Spinal Fluid Findings in Anicteric Cases Without Central Nervous System Manifestations*

Case No.	Day of Disease	Color of Fluid	Total Cells	P. M. N., %	Lymphocytes, %	Proteins	Sugar	Chlorides	Leptospirae
29	8	Cloudy	1,200	63	37	140	61	--	--
30	4	Clear	10	0	100	14	88	--	No
31	6	Clear	8	0	100	10	66	--	No
32	5	Clear	2	0	100	18	83	680	No
33	6	Clear	2	50	50	23	101	--	--
34	4	Clear	2	0	100	29	62	--	No
35	3	Clear	1	0	100	14	81	--	No
36	5	Clear	1	0	100	37	--	--	No
37	6	Clear	0	0	0	10	79	--	No
38	4	Clear	0	0	0	10	79	--	No
39	6	Clear	0	0	0	14	123	--	No
40	5	Clear	0	0	0	10	86	--	No

the third to eighth days of illness, only one showed definite changes in the spinal fluid (Table 8). This patient complained of myalgia, headache, conjunctival inflammation, and high fever. The clinical findings were identical to the other anicteric cases tested. However, the spinal fluid findings deserve a detailed evaluation, and the case is presented in detail.

Case of Anicteric Leptospirosis Without Signs of Meningitis and Definite Spinal Fluid Alterations

A 13-year-old white Puerto Rican boy suddenly developed severe general malaise, muscle pains, chills, fever, headache, nausea, and vomiting. On the third day of illness he was acutely ill but well oriented and he had a temperature of 105 F, a pulse rate of 120 and respirations of 24 per minute, and a blood pressure of 120/70 mm. Hg. The pharynx was injected; a soft blowing systolic murmur was heard over the pulmonic and mitral areas, and exquisite tenderness was elicited on pressure in the large muscle masses. No signs of meningeal irritation were present. He was admitted with a presumptive diagnosis of acute rheumatic fever.

The hemoglobin values varied from 10.4 to 11.4 gm. per 100 cc. of blood, and the erythrocyte count, from 3,910,000 to 4,260,000 per cubic millimeter. The leukocyte count on admission was 9,200, with 86% polymorphonuclear cells and 14% lymphocytes. Subsequent, white cell counts ranged from 5,300 to 6,150, with a normal distribution. Blood smears for malaria, as well as repeated blood cultures, were negative. A throat culture showed α-hemolytic Streptococcus and nonhemolytic Staphylococcus pyogenes var. albus. Repeated urinalyses and urine cultures were negative. The stools revealed ova of Ascaris lumbricoides. The electrocardiogram and radiographic studies of the chest and sinuses were reported as normal. Serologic tests for syphilis, Brucella, typhoid, paratyphoid, typhus, and psittacosis were negative. The complement-fixation test for leptospirosis was positive on the 10th day of illness. On the eighth day, a lumbar puncture revealed a cloudy spinal fluid, which contained 1,200 cells per cubic millimeter, with 63% polymorphonuclear leukocytes, total proteins of 140 mg. %, and 61 mg. of glucose. A spinal fluid examination on the 14th day showed

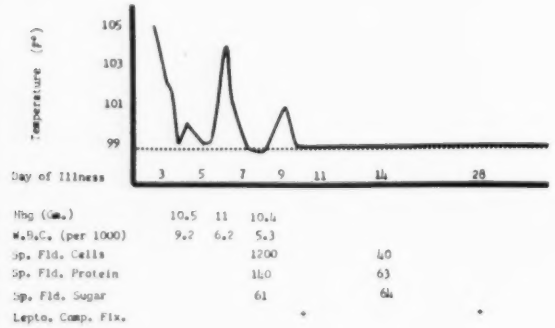

Chart 2.—A case of anicteric leptospirosis with meningitis and without central nervous system manifestations.

40 cells per cubic millimeter, 63 mg. of protein, and 64 mg. of sugar.

The fever subsided spontaneously shortly after admission, to reappear on the sixth day of illness, when it was accompanied by a moderate conjunctivitis. These phenomena persisted until the 10th day of illness, when the muscular pains, headache, and cardiac murmurs disappeared. No beneficial effects were observed from therapy with penicillin and sulfadiazine. Although the headache was moderately severe, no signs of meningeal irritation were ever elicited (Chart 2).

Comment.—The most striking feature of this case was the definitely abnormal spinal fluid in the absence of clinical evidence of meningeal involvement. The cephalalgia was of only moderate intensity, perhaps, not as severe as in many other cases of leptospirosis with normal spinal fluids. This was an acute febrile illness of sudden onset with generalized systemic manifestations and with cardiac murmurs suggesting the diagnosis of acute rheumatic fever. It is evident that the latter diagnosis was properly ruled out. The saddle-shaped temperature curve, the appearance of conjunctivitis, and the persistence of myalgia led to the suspicion of leptospirosis. It must be emphasized that the results of the spinal fluid examination were unexpected.

Comment

Although the classical clinical picture of leptospirosis with jaundice (Weil's disease) is easily recognized by most physicians, the diagnosis of the disease in the preicteric phase or in the anicteric form generally presents serious difficulties, for, at times, it is easily mistaken for murine typhus, dengue fever, typhoid, severe influenza, acute rheumatic fever, and septic meningitis. However, there are some early symptoms that may increase the diagnostic accuracy in the anicteric forms: an acute, explosive onset, with chills, a rapidly rising fever, intense conjunctivitis with photophobia but little, if any, lacrimation, intense myalgia, and severe headache, frequently accompanied by nausea and vomiting. This clinical picture is rendered more significant when it occurs in people living among rats and when contact with contaminated stagnant water is possible. The great majority of cases are recorded mainly in young adults after a heavy rainfall. It is emphasized that the diagnosis of leptospirosis should be contemplated in any patient presenting the symptoms of severe influenza without definite signs of an upper respiratory infection.[29]

There is enough clinical and experimental proof to demonstrate that the disease is initiated by a state of leptospiremia, which generally persists during the first week. During this period (preicteric phase), alarming systemic manifestations may appear, presumably due to an overwhelming toxemia. It seems as if disappearance of the organisms from the blood is followed by tissue localization, with growth and multiplication of the leptospirae in the liver, kidney, brain, heart, etc., with symptoms and signs related to the most seriously affected organs. It has been suggested that no tissue escapes from the ravages of certain pathogenic leptospirae.

It appears as if the intensity of involvement of specific tissues and organs governs the degree of the severity of the localizing symptoms and signs in the latter stages of the disease. Disturbances in function of these organs may give rise to a generalized toxemia from uremia and/or hepatic insufficiency. The disease is accompanied by varying degrees of vascular damage, which may be an important factor in the issue of life or death. Death from massive gastrointestinal bleeding presumably occurs as a result of a direct effect of the leptospirae in the blood vessel wall. The possibility of bleeding from other areas is emphasized. Thus, hemorrhagic pneumonitis is commonly observed in the severest forms of Weil's disease.[30] Furthermore, the frequent bleeding into the skin and mucous membranes (petechiae and ecchymosis) does not appear to be governed by the coexistent hepatic insufficiency (hypoprothrombinemia). The diffuse vascular fragility secondary to uremia does not seem to be an important

contributing factor, inasmuch as the various degrees of hemorrhagic diastheses may occur in both the icteric and the anicteric cases, with or without signs of renal failure.[29]

In infections due to Leptospira pomona and Leptospira mitis, the clinical picture is generally dominated by meningeal manifestations indistinguishable from those of the milder forms of "aseptic meningitis." Those with Leptospira autumnalis are characterized by a clinical picture similar to influenza and are generally accompanied by skin manifestations in the pretibial area (pretibial fever, Fort Bragg fever), with a rapid recovery with supportive therapy.[24] The extremely low fatality rate and the lack of pathological material from humans affected by these leptospirae render an evalution of the alterations of the different tissues and organs impossible. Awaiting further pathological studies on this subject, it would be plausible to assume that perhaps the only forms of leptospiral meningitis are those due to L. pomona and L. mitis.[31,32]

Serious pathological alterations, resulting in subarachnoid hemorrhage, paralysis of the cranial nerves, and symptoms and signs indistinguishable from bulbar poliomyelitis, may arise with infection with L. icterohaemorrhagiae.[33] Besides, there have been reports of transverse myelitis in the severest cases. These central nervous system alterations are generally accompanied by extensive hepatic, renal, and, at times, cardiac dysfunction. The commonest and, fortunately, the mildest of all forms of central nervous system alterations are those of meningitis. These may occur in classical Weil's disease or in the more benign anicteric forms.

An analysis of our data tends to indicate that although meningeal irritation is rather common in infections with L. icterohaemorrhagiae, clear-cut clinical signs of meningitis, which may serve as indications for the investigation of the spinal fluid, were encountered in approximately one-half of this selected group of cases. However, alterations in the spinal fluid are frequently present in those without signs of meningeal involvement, showing that pleocytosis, increased proteins, and even the presence of leptospirae in the spinal fluid may occur early in the course of the disease without significant clinical indications for a lumbar tap. Thus, it seems as though this phenomenon is not governed by the degree of severity of the disease, since many of the cases were anicteric. Perhaps the early examination of the spinal fluid in both icteric and anicteric forms of the disease is of only diagnostic rather than prognostic value, since it has been shown that cultures of the fluid during the first week of illness serves as an efficient method for the isolation of the leptospirae.

Our results indicate that xanthochromia of the spinal fluid is of limited diagnostic value in classical Weil's disease. Although an analysis of such a limited sample may not warrant definite conclusions, the appearance of the spinal fluid does not seem to be a dependable criterion for the diagnosis of the disease even in the most intensely jaundiced cases.

The lack of correlation between the serum bilirubin values and the color of the spinal fluid would favor something other than the level of circulating conjugated bilirubin as the most important governing factor of this phenomenon. It is plausible to assume that perhaps the most important disturbance may reside in the degree of permeability of the capillary and meningeal membranes. The possible role of the frequent extravasations of blood in the pathogenesis of the xanthochromia of the spinal fluid remains unassessed. Perhaps the absence of erythrocytes would tend to minimize its significance, since it would eliminate the possibility of significant subarachnoid bleeding.

There are extreme limitations in the interpretation of the physical signs pointing to meningeal irritation in leptospirosis. All patients suffer from intense myalgia involving, among other muscles, those of the neck and back. Presumably, false-positive signs of neck rigidity are frequently encountered, and the diagnosis of meningitis should rest

on the examination of the spinal fluid, with an attempt at the isolation of the leptospirae. On the other hand, a turbid spinal fluid, with a cell count as high as 1,200 per cubic millimeter and high protein content, may be found in anicteric leptospirosis without signs of meningitis. It seems to us as if the final evaluation of the extent of meningeal involvement belongs to the pathologist, since most of the severe neurological manifestations may be produced or at times masked by the intense renal, vascular, and hepatic alterations of the disease.

Summary

An analysis of the data indicates that the clinical signs of meningeal irritation in infections with the Leptospira icterohaemorrhagiae may be vitiated by the intense myalgia that usually accompanies the disease. In some instances, unequivocal laboratory evidence of meningitis may be encountered despite the absence of definite clinical signs and the leptospires may be isolated from otherwise normal spinal fluids if lumbar punctures are performed early in the course of the disease.

The pathogenesis of the central nervous system manifestations may be governed by various factors, including the diffuse or focal pathologic alterations attributed to the direct or indirect effect of the leptospirae; diffuse vascular damage, disturbances in electrolyte balance, intense hepatic alterations, and/or renal failure.

The spinal fluid alterations are of no apparent prognostic value. However, the most pronounced changes are generally encountered among those cases of classical Weil's disease with severe renal failure. In these, hypotension and coma are very serious prognostic signs.

In some instances, the meningeal manifestations may appear as the most dominant feature of the disease either prior to the onset of icterus or among the anicteric cases. These phenomena call for a refined diagnostic accuracy and an increased level of suspicion of the disease.

The examination of the spinal fluid in the light of the clinical picture may aid in the establishment of the diagnosis of the disease through the isolation of the leptospirae. However, a bilirubin-tinged spinal fluid is of limited diagnostic value, since a clear fluid is the rule even in the presence of high serum bilirubin levels.

The pathogenesis of xanthochromia of the spinal fluid in classical Weil's disease remains unexplained. It may be governed by an increased capillary and meningeal permeability from either the direct effect of the leptospirae or the complicating renal failure.

It must be emphasized that the anicteric form of leptospirosis is at times indistinguishable from other acute infectious diseases, mainly severe influenza without prominent signs of an acute respiratory infection. Since most of these may be accompanied by symptoms suggesting either meningitis or encephalitis, the final diagnosis must depend on laboratory confirmation. The evaluation of the extent of the cerebral and meningeal involvement in leptospirosis properly belongs to the pathologist.

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The Syndrome of Chronic Pulmonary Disease and Gastroduodenal Ulceration

A Clinical Study and Literature Review

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Introduction

This hospital located in the heart of West Virginia's coal industry has an unusually large number of patients with chronic pulmonary disease. The recent literature contains several articles suggesting an increased incidence of gastroduodenal ulceration in these patients.[1-3]

We have had the clinical impression that patients with chronic pulmonary disease tend to have gastroduodenal ulceration more frequently than would be anticipated in the general population. To justify this impression, this study is presented.

Material and Method

The charts of all patients admitted to the medical teaching service from January, 1955, through April, 1958, were reviewed. There were 845 patients. This was considered a random sampling of general medical patients. The following information was abstracted from the records: (1) age, race, and sex; (2) symptoms, signs, x-ray, electrocardiographic, and laboratory evidence of *chronic pulmonary disease*,* and (3) symptoms, complications, and x-ray evidence of *gastroduodenal ulceration*.†

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* By chronic pulmonary disease we mean one or a combination of chronic asthmatic bronchitis, emphysema, bronchiectasis, and pulmonary fibrosis. Specific pulmonary disease, e. g., granulomas, fungus infections, cystic disease, and primary or metastatic lung cancer, were not included. Cardiac causes of chronic pulmonary disease, e. g., mitral stenosis, were not included.

† By gastroduodenal ulceration we mean benign gastric ulcer, duodenal ulcer, and hypertrophic gastritis.

Many of these patients were managed by one of us, but to evaluate the records properly, it was thought that certain criteria had to be set up.

Criteria for Diagnosis of Chronic Pulmonary Disease.—(1) Symptoms: Chronic productive or nonproductive cough with or without wheezing, history of asthma, and dyspnea.

(2) Signs: Increased anteroposterior diameter of the chest, depressed relatively immobile diaphragms, hyperresonance to percussion, distant breath sounds, rales and ronchi, wheezing, and cyanosis.

(3) Chest X-Ray: Increased peribronchial thickening, bronchiectasis (also by bronchogram), increased radiolucency of lung fields, widened intercostal spaces, low diaphragms, vertical heart position, and parenchymal fibrosis.

(4) Electrocardiogram: Clockwise rotation in a vertical heart, P-pulmonale, right axis deviation, ST- and T-wave changes in V_1-V_3, right bundle-branch block, and right ventricular hypertrophy.

5. Laboratory: Increased hemoglobin and hematocrit; decreased serum chloride and increased carbon dioxide-combining power in the absence of a metabolic alkalosis.

Not all of the above criteria needed to be present in any given person, but at least three out of five were necessary before the diagnosis of chronic pulmonary disease was made.

Criteria for Diagnosis of Gastroduodenal Ulceration.—(1) Gastroduodenal X-Ray: Benign gastric ulcer, duodenal ulcer, pyloroduodenal irritability, deformity of the duodenal cap, subtotal gastrectomy and/or gastroenterostomy, and hypertrophic gastritis.

(2) Histological and/or surgical demonstration of an ulcer.

(3) Past history of subtotal gastric resection for peptic ulcer.

Results

Of the 845 patients, there were 195 (23.1%) with chronic pulmonary disease; 72 (8.5%) with duodenal ulcer; 12 (1.4%)

TABLE 1.—*Breakdown of Number of Diseases*

	No.	%
Total no. of patients	845	
Chronic pulmonary disease	195	23.1
Duodenal ulcer	72	8.5
Benign gastric ulcer	12	1.4
Hypertrophic gastritis	8	0.9

with benign gastric ulcer, and 8 (0.9%) with hypertrophic gastritis (Table 1).

Chronic Pulmonary Disease.—Of the 195 patients with chronic pulmonary disease, 160 (82%) had emphysema. There were 124 males and 71 females, 175 (90%) over the age of 40. Electrocardiographic evidence of chronic cor pulmonale was present in 41 patients. There were a great many other patients with clinical cor pulmonale, but the electrocardiograms either were not done, were normal, were nonspecific, or showed left bundle-branch block or atrial fibrillation. Chest x-rays were done in 190 of these patients; 135 had electrocardiograms, and 90 had gastroduodenal x-rays. The majority of these patients smoked cigarettes, but this aspect was not quantitated.

There were 92 patients with *gastroduodenal ulceration*. Duodenal ulcer was present in 72; benign gastric ulcer, in 12, and hypertrophic gastritis, in 8. There were 53 males and 39 females, 72 (78%) over the age of 40.

Chronic Pulmonary Disease Associated with Gastroduodenal Ulceration.—This occurred in 54 patients. There were 51 patients with peptic ulcer (47 duodenal and 4 benign gastric) and 3 with hypertrophic gastritis. The incidence of peptic ulcer in chronic pulmonary disease is 25.6% in this series. If hypertrophic gastritis is included, the incidence is 27.7%. There were 36 males and 18 females, 46 (85%) over the age of 40. Ulcer symptoms in this group were typical in 32, atypical in 12, and absent in 7. There were 15 complications: hemorrhage 12, perforation 1, and hemorrhage and obstruction 2. There were 105 patients with chronic pulmonary disease who did not have gastroduodenal x-rays. Of these, 10 had ulcer symptoms; 2 were typical with 1 bleeding, and 8 were atypical.

TABLE 2.—*Comparison of Two Groups of Patients*

	Gastroduodenal Ulceration Alone (No.)	Chronic Pulmonary Disease & Gastroduodenal Ulceration (No.)
Patients	48	54
M : F	17:21	36:18
Over age 40	26 (68%)	46 (85%)
Symptoms:		
Typical	25 (66%)	32 (59%)
Atypical	7	12
Absent	6	7
Complications:	11 (30%)	15 (28%)
Hemorrhage	10	12
Perforation	0	1
Hemorrhage & obstruction	1	2

There were 38 patients with gastroduodenal ulceration not complicating chronic pulmonary disease. There were 17 males and 21 females, 26 (68%) over the age of 40. These patients exhibited about the same symptomatology as those associated with chronic pulmonary disease and about the same percentage of complications. Table 2 compares these two groups of patients.

Of the 41 patients with electrocardiographic evidence of chronic cor pulmonale, 17 had gastroduodenal x-rays. There were seven men and one woman, all over the age of 40. Eight patients had duodenal ulcer (20%). Four of these were bleeding. Symptoms were typical in four, atypical in two, and absent in two. Seven of these patients were over the age of 40.

Comment

The incidence of peptic ulcer in the general population is 5%-10%.[4] In 700 consecutive autopsies, Green and Dundee[1] noted a 6.4% incidence of peptic ulcer. This clinical series shows about 10%. The incidence of peptic ulcer in patients with chronic pulmonary disease is 25.6% in this series. This figure is statistically significant when the χ^2 rule is applied. Others have found this relationship to range between 18.8% and 33.1%.[1-3,5] (Table 3). It is

TABLE 3.—*Relationship Between Chronic Pulmonary Disease and Peptic Ulcers*

	Chronic Pulmonary Disease, No.	Peptic Ulcer, No.	Incidence, %
Plotkin	130	43	33.1
Lowell et al.	25	6	24.0
Franklin et al.	58	13	22.4
Green & Dundee	64	12	18.8
Green & Dundee	72	14	19.4
This series	195	51	25.6
Total	544	139	25.6

interesting that our figure is the same as the average of all six series of patients. In 1951, Martii Hirvonen[6] noted the more frequent occurrence of pulmonary emphysema in cases of gastric ulcer. In 1955, Weber and Gregg[7] noted that over 40% of 70 cases of benign gastric ulcer were complicated by chronic pulmonary disease.

How do we account for such an increased incidence? Many theories have been proposed to help explain the etiology and pathogenesis of this syndrome. Plotkin,[2] and Weber and Gregg[7] have summarized some of these. Many of the factors commonly producing peptic ulceration most certainly must be eccentuated in these patients. Kirsner's[8] article refers to many of these. *Hyperacidity* and *decreased tissue resistance* seem to be the common denominators. How do these pathological changes develop in patients with chronic pulmonary disease? There are probably multiple causes. These will be listed and commented upon.

Hyperacidity.—1. Increased Corticosteroid Activity: (*a*) Chronic stress both due to respiratory embarrassment and the relatively high incidence of emotional illness present in West Virginia coal miners.[9] (*b*) Administration of corticotropin and corticosteroids. (*c*) Administration of sympathomimetic amines, e. g., epinephrine, ephedrine, and isoproterenol (Isuprel). (*d*) Administration of salicylates. These factors stimulate or compliment the hypothalamic-pituitary-adrenal axis, resulting in hyperacidity and often increased pepsin activity. Plotkin[2] noted that most of these patients exhibited eosinopenia, a persistent highest elevation of blood sugar at one hour instead of the normal one-half hour in the glucose-tolerance test, and a high free and total gastric acidity.

2. Increased Endogenous Histamine Production: Increased amounts of histamine are produced both in atopic and nonatopic asthma. Cell damage due to various causes, e. g., hypoxia and infection, is associated with increased histamine concentration and liberation. This stimulates gastroduodenal smooth muscle contraction and gastric acid secretion.[10]

3. Tobacco Smoking: A significant number of these patients smoke cigarettes.[3] Nicotine causes an increase in gastric acidity.[11]

4. Increased Activity of the Carbonic Anhydrase System: Owing to chronic hypercapnia with its resultant respiratory acidosis, there is an increase in carbonic anhydrase activity in the parietal cells of the stomach.[12,13] This is followed by an increase in hydrogen ion concentration. By the *Law of Mass Action*, hyperacidity may be expected.

5. Administration of Rauwolfia Serpentina and Its Alkaloids: These drugs are given occasionally to patients with chronic pulmonary disease for their sedative and antihypertensive properties. These drugs, if given in significant amounts, especially parenterally, cause a marked and sustained rise in gastric acidity.[14-16]

Decreased Tissue Resistance.—1. Local Gastroduodenal Irritants: The patient with chronic pulmonary disease is subject to a host of oral medication. Some of these are gastroduodenal irritants, e. g., saturated solution of potassium iodide, ammonium chloride, salicylates, theophylline preparations, and chlortetracycline (Aureomycin).

2. Increased Corticosteroid Activity: This produces increased protein catabolism and decreased fibroplasia, thereby decreasing tissue resistance.

3. Arteriosclerosis: Since most of these patients are in the older age group, with

its inherent arterial disease, tissue vitality is diminished.

4. Visceral Hypoxia: This is due to the respiratory insufficiency, increased venous pressure, and polycythemia if present.

5. Malnutrition: A significant number of these patients are in negative nitrogen balance and exhibit hypovitaminosis due to inadequate food intake and increased corticosteroid activity. They present a typical picture of barrel chest and wasted limbs.

Many of the above factors are peculiar to patients with chronic pulmonary disease and logically should render them more susceptible to gastroduodenal ulceration than would be expected in the general population. Of course, these patients are also susceptible to the other etiological and pathogenetical factors in peptic ulcer.

In this series, symptoms and complications of ulcer were similar in gastroduodenal ulceration alone and in association with chronic pulmonary disease. However, in the latter group, the patients were in an older age group and men predominated over women two to one. It has been noted that symptoms of ulcer in patients with chronic pulmonary disease were frequently atypical or absent.[2]

It seems that gastroduodenal x-rays should be performed on all patients with chronic pulmonary disease, since a significant number have atypical or no ulcer symptoms. Of the 195 patients with chronic pulmonary disease, 90 (46%) had gastroduodenal x-rays. Many of these patients were too ill for x-ray study. Of these ninety, fifty-four (60%) showed gastroduodenal ulceration. There seems to be no correlation between the incidence of gastroduodenal ulceration and the severity of the chronic pulmonary disease.

It was noted that 41 patients in this group of 845 had Laennec's cirrhosis, 9 of whom had peptic ulcer. Of these nine, four had chronic pulmonary disease. To our knowledge, this factor has not been emphasized in the many articles on the association of cirrhosis and peptic ulcer. It seems reasonable to assume that chronic pulmonary disease may contribute as much to the development of ulcer in patients with cirrhosis as does cirrhosis itself.

Patients with uncomplicated chronic pulmonary disease with chronic hypoxia often have a normal or increased hemoglobin and hematocrit. If anemia is present and the signs of increased blood destruction and decreased blood formation are ruled out, a bleeding peptic ulcer should be suspected. This should also be suspected in any patient exhibiting melena who has chronic pulmonary disease, regardless of atypical or absent ulcer symptoms.

Because of the relatively peculiar pathogenesis of this syndrome, both prophylactic and therapeutic measures may be instituted with ease to combat hyperacidity and decreased tissue resistance. Forced or supplementary feedings would help restore positive nitrogen balance and decrease gastric acidity. If gastroduodenal symptoms are present, antacids may be added. If an ulcer is found, active therapy should be started. Anticholinergic drugs should be used with discretion due to the drying effect on tracheobronchial mucus.

Drugs commonly utilized in the treatment of chronic pulmonary disease become more of a problem, owing to the increased incidence of gastroduodenal ulceration in these patients. Most of these patients need bronchodilators, expectorants, antibiotics, sedation, and, at times, anti-inflammatory agents. These drugs are necessary and often life-saving and should be utilized, but their pathophysiological effects should be understood and appreciated.

Summary

The records of a random group of 845 general medical patients are reviewed. A statistically significant increase in the incidence of gastroduodenal ulceration in patients with chronic pulmonary disease was found. This incidence was 27.7%. The etiology and pathogenesis are discussed.

The majority of these patients were men over the age of 40. Ulcer symptoms and complications were similar in these patients

and in patients with gastroduodenal ulceration alone. The severity of the pulmonary disease did not correlate with the incidence of chronic gastroduodenal ulceration.

Every patient with chronic pulmonary disease should have gastroduodenal x-ray studies and examination of the stool for occult blood. If a patient with chronic pulmonary disease is anemic, a bleeding peptic ulcer should be expected.

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Addendum

There were 43 patients admitted to the medical teaching service in May and June, 1958. There were 12 patients with chronic pulmonary disease (the majority being obstructive emphysema), 5 with duodenal ulcer, and 1 with benign gastric ulcer.

Of this group, there were five patients having chronic pulmonary disease and gastroduodenal ulceration (four duodenal and one benign gastric). There were four men and one woman in this group, all over the age of 40.

With these additional data, the incidence of gastroduodenal ulceration in patients with chronic pulmonary disease approaches 29%.

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Hyperventilation Syndrome

Changes in the Electrocardiogram, Blood Gases, and Electrolytes During Voluntary Hyperventilation; Possible Mechanisms and Clinical Implications

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The symptom patterns of the hyperventilation syndrome have been recognized for many years.[1-5] Some workers have reported abnormal lowering or inversion of the T-wave and, less frequently, depression of the ST segment in the routine electrocardiogram of many patients with this syndrome or with anxiety and emotional instability.[6-13] These changes are readily reproduced by voluntary hyperventilation. Several others have observed similar changes of the T-wave in the electrocardiogram of certain normal persons during voluntary hyperventilation.[14,15]

The purpose of this report is (1) to describe the electrocardiographic abnormalities during voluntary hyperventilation in 20 patients with the hyperventilation syndrome and the effects of inhalation of CO_2 and administration of various drugs in these changes; (2) to present the changes of serum electrolytes, respiratory gases, and pH of the blood in these patients during hyperventilation, with or without inhalation of CO_2; (3) to postulate a possible mechanism for the electrocardiographic changes, and (4) to emphasize their clinical implications.

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Methods and Material

Twenty patients were studied. Sixteen were female and four male. Their ages ranged from 20 to 55 years. Careful study failed to disclose organic heart disease in all but one patient who had a small interatrial septal defect confirmed by cardiac catheterization. In all patients, studies were carried out about two hours after a meal. An indwelling needle was inserted into a brachial artery for sampling of blood. Electrocardiograms were made with the patients recumbent. After a tracing was made at rest, the patient breathed forcibly and rapidly for one to three minutes. An electrocardiogram (V_4 or V_5) was recorded continuously throughout the periods of hyperventilation and recovery. In most instances, hyperventilation was repeated 10-20 minutes later. Subsequently, hyperventilation was again repeated, this time with the patient breathing 6% CO_2. The ventilatory rate was measured by a wet-test gas meter and in each case exceeded 25 liters per minute.

While the electrocardiogram was recorded, samples of arterial blood were obtained for analysis of pH, respiratory gases, and electrolytes during periods of control, hyperventilation with room air, and hyperventilation with 6% CO_2. In five patients, serum glutamic oxalacetic transaminase activity was also determined.

An electrocardiogram was taken during intravenous infusion of 20μg. of epinephrine in five patients. In four of these, the study was repeated after an intravenous injection of 5 mg. of phentolamine (Regitine). Similar studies were made in five patients during the intravenous infusion of 20-30 mEq. of potassium chloride over 20 minutes, followed by voluntary hyperventilation and finally by 20μg. of intravenous epinephrine.

Electrocardiograms were recorded during hyperventilation in three patients who had received 30 mg. of propantheline (Pro-Banthine) intravenously about 30 minutes previously. In two patients, an electrocardiogram was made during hyper-

ventilation immediately following sublingual administration of 0.3 mg. of glyceryl trinitrate (nitroglycerin). In eight patients, the electrocardiogram was recorded during exercise on a motor-driven treadmill, usually on the day of study of hyperventilation.

Serum potassium and sodium were determined by a flame photometer[16]; serum chloride, by the method of Schales and Schales,[17] and serum glutamic oxalacetic transaminase, according to the method of Karmen, Wroblewski, and LaDue.[18] The determination of serum calcium and its ultrafiltrable portion was made by the method of Toribara and Terepka.[19] Arterial blood oxygen content, capacity, and saturation were determined by the method of Peters and Van Slyke.[20] Arterial blood gas tensions were directly measured by the method of Riley and associates.[21] Arterial blood pH was analyzed in a Cambridge pH meter according to the method of Wilson.[22]

Two patients who had classical symptoms of hyperventilation syndrome did not exhibit abnormal changes in the electrocardiogram either at rest or during voluntary hyperventilation. Therefore, their data are not included in this report.

Results

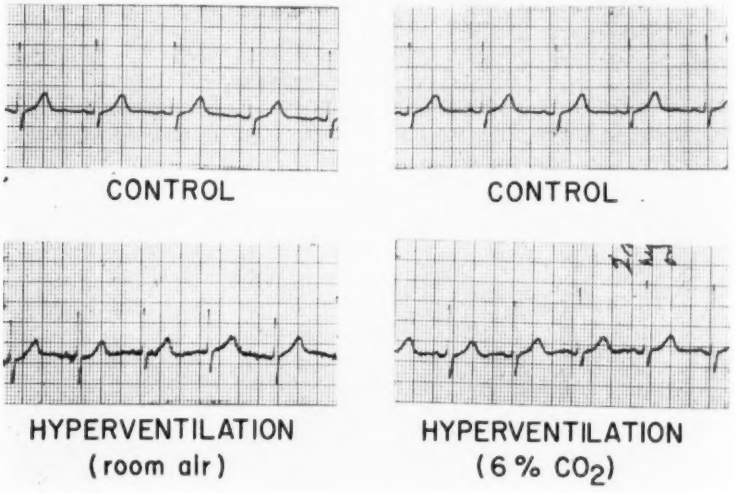
The presenting symptoms of 20 patients with the hyperventilation syndrome are summarized in Table 1.

TABLE 1.—*Presenting Symptoms of Twenty Patients with the Hyperventilation Syndrome*

Symptom	No.
Cardiac	
Atypical chest pain	20
Palpitation	
Respiratory	
"Exertional dyspnea"	15
Central nervous system	
Faintness	4
Peripheral	
Tingling & numbness	4
Gastrointestinal	
Bloating & belching	4
Psychic	
Fatigue	6
Insomnia & "nervousness"	6
"Exhaustion"	2

No significant change in the electrocardiogram of 10 normal subjects was observed during or following hyperventilation with room air or 6% CO_2 (Fig. 1). Fifteen patients with the hyperventilation syndrome exhibited transient inversion of T-waves (Fig. 2). Two showed depression of ST segments (Fig. 3), and two others showed reduction in amplitude of the T-wave and marked prolongation of the Q-T interval (Fig. 4). In one patient, an initially in-

Fig. 1.—Patient 19, a 51-year-old man. Electrocardiograms recorded during hyperventilation with room air and with 6% CO_2 in a control subject. Note no change in either T-wave or ST segment.



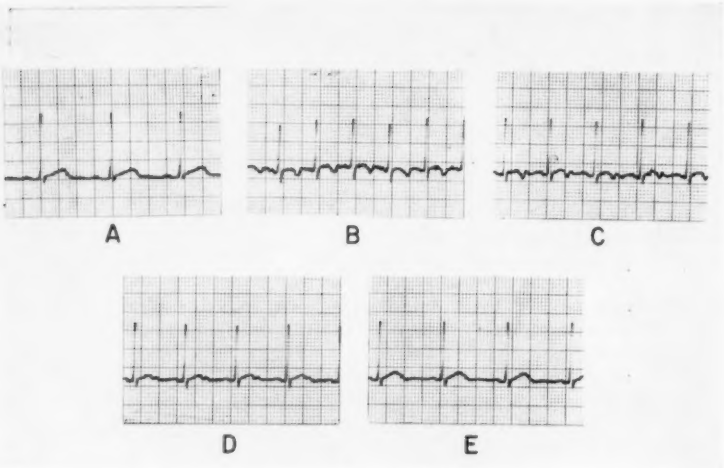
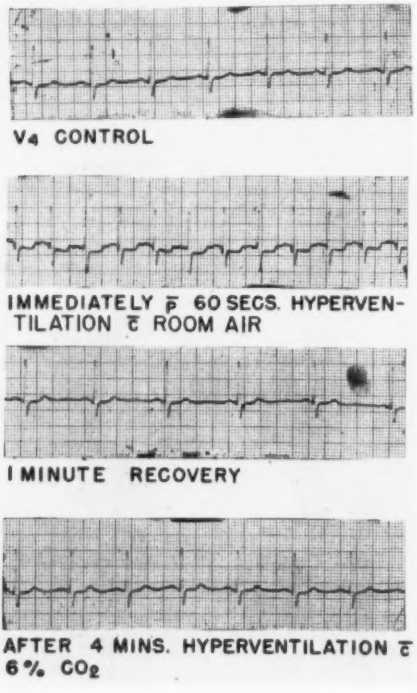


Fig. 2.—Electrocardiographic tracings in Patient 18, a 27-year-old man. *A*, during control period. *B*, during hyperventilation. *C*, immediately after hyperventilation. *D*, one minute after hyperventilation. *E*, two minutes after hyperventilation.

Fig. 3.—Electrocardiogram of Patient 4, showing depression of ST segment during hyperventilation with room air and no change during hyperventilation with 6% CO_2.



verted T-wave became upright during hyperventilation (Fig. 5).

In Table 2 are presented the results of analysis of respiratory gases and pH and electrolytes of the blood during periods of control (Period 1), hyperventilation with room air (Period 2), and hyperventilation with 6% CO_2 (Period 3). The values of the serum calcium and glutamic oxalacetic transaminase are given in Table 3.

No significant change was found in the concentrations in the serum of sodium, chloride, calcium, and transaminase. Arterial blood oxygen saturation and tension were usually slightly higher during hyperventilation than during control periods. There was little or no change in the oxygen capacity of the blood.

On the other hand, as shown in Table 2 and Figure 6, significant changes were observed in arterial CO_2 tension, CO_2 content, pH, and serum potassium from Period 1 to Period 2 and from Period 2 to Period 3. The direction of change from one period to another was the same in every instance, and the changes were statistically highly significant.

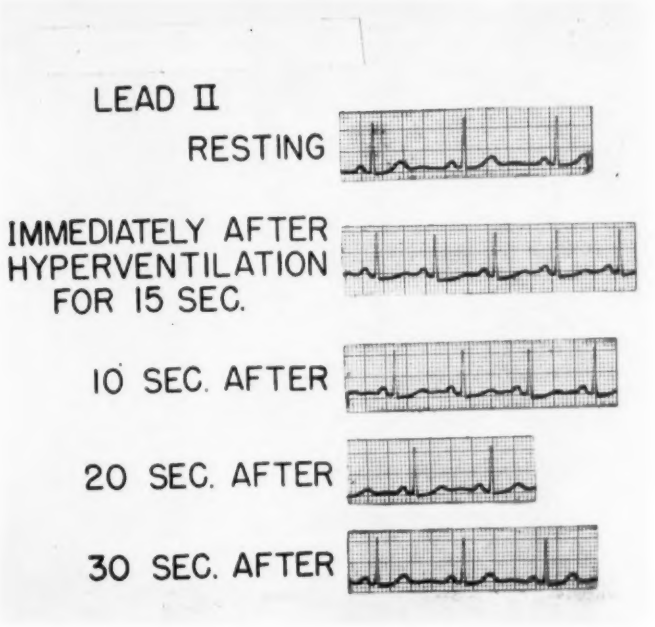
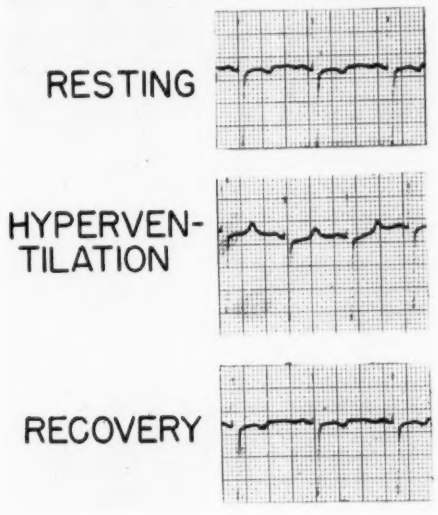


Fig. 4.—Electrocardiogram of Patient 20, a 45-year-old woman, showing transient lowering of the T-waves and marked prolongation of Q-T interval immediately after hyperventilation.

The serum potassium in blood from the coronary sinus of one patient was 4.1 mEq. per liter during the control period, increasing to 5.2 mEq. per liter during hyperventilation.

Fig. 5.—Electrocardiogram of Patient 11, a 38-year-old man, showing initially inverted T-waves, which became upright during hyperventilation.



Hyperventilation with 6% CO_2 prevented the electrocardiographic changes in all but one patient. A representative tracing is shown in Figure 7.

Following intravenous infusion of potassium chloride, the electrocardiographic changes during hyperventilation were completely prevented in four patients and partly in another. Changes in arterial blood CO_2 tension, CO_2 content, and pH during hyperventilation were about the same whether or not potassium was infused. The concentration of serum potassium was slightly higher than usual in three of five patients receiving the potassium infusion.

In five patients, intravenous epinephrine produced changes in the electrocardiograms within one minute which were similar to those observed during hyperventilation with room air. Figure 8 demonstrates the electrocardiographic changes in Patient 18 during hyperventilation as well as intravenous injection of epinephrine. The reproducibility of the electrocardiographic changes during

TABLE 2.—*Gas Analysis, pH, and Electrolytes of Arterial Blood Obtained from Eighteen Patients with the Hyperventilation Syndrome*

Patient	Age & Sex	Periods of Study *	$PaCO_2$ †	$CaCO_2$ ‡	pH	Sao_2 §	Potassium	Sodium mEq/L.	Chloride
1	35	I	46	22.9	7.38	96.4	3.8	--	--
	F	II	25	18.6	7.62	99.2	4.3	--	--
		III	38	23.0	7.51	100.0	3.9	--	--
2	44	I	40	20.2	7.42	95.2	3.6	140	--
	F	II	22	15.6	7.60	97.4	3.8	138	--
		III	46	21.7	7.37	98.5	3.4	138	--
3	41	I	47	24.1	7.34	94.1	4.0	--	--
	F	II	32	20.5	7.49	99.4	4.9	--	--
		III	47	23.7	7.33	100.8	4.1	--	--
4	55	I	48	23.8	7.40	92.0	3.8	141	--
	F	II	27	18.8	7.58	99.7	4.3	141	--
		III	38	24.0	7.42	100.1	4.1	141	--
5	42	I	36	21.5	7.46	96.2	3.9	143	--
	F	II	28	18.0	7.54	98.6	4.2	138	--
6	42	I	44	23.0	7.44	93.5	4.3	142	--
	M	II	30	18.5	7.52	98.1	4.8	148	--
7	27	I	36	18.7	7.36	96.5	4.1	--	--
	F	II	27	16.2	7.51	97.4	4.5	--	--
		III	40	20.6	7.43	97.9	3.9	--	--
8	40	I	33	22.5	7.39	95.3	4.3	138	--
	F	II	27	18.1	7.52	100.0	4.8	138	--
		III	47	23.7	7.36	96.5	4.3	137	--
9	31	I	37	22.8	7.39	97.6	4.3	138	--
	F	II	25	19.0	7.54	99.7	4.9	140	--
		III	36	23.1	7.42	101.5	4.2	140	--
10	48	I	42	21.6	7.40	93.7	4.4	138	108
	M	II	32	18.1	7.49	100.4	4.7	137	108
11	37	I	--	21.5	--	--	4.5	140	107
	M	II	--	17.0	--	--	4.9	138	108
12	37	I	34	21.5	7.39	92.7	3.4	141	114
	F	II	20	17.6	7.51	100.0	3.6	143	114
		III	43	23.4	7.25	98.8	3.1	135	112
13	20	I	41	21.6	7.39	95.0	3.9	141	106
	F	II	25	19.2	7.51	98.7	4.4	142	113
		III	48	23.0	7.36	99.7	4.0	143	108
14	55	I	46	24.3	7.37	93.8	4.3	141	102
	F	II	30	21.3	7.59	95.8	4.9	142	101
		III	44	24.9	7.42	98.2	4.7	144	101
15	41	I	46	22.6	7.36	99.2	3.9	142	116
	F	II	23	16.6	7.61	95.3	4.7	139	120
		III	44	22.3	7.41	103.0	4.2	142	115
16	38	I	41	19.7	7.39	95.7	4.0	146	110
	F	II	25	16.4	7.56	98.6	4.5	146	108
		III	40	21.2	7.44	99.3	3.8	146	110
17	24	I	40	21.4	7.40	96.3	3.2	138	--
	F	II	24	17.3	7.57	101.6	3.9	139	--
		III	--	21.9	--	99.2	--	140	--
18	26	I	45	22.6	7.44	99.0	4.4	151	110
	M	(A) II	20	17.3	7.68	96.0	5.8	144	114
		III	40	22.7	7.48	97.0	4.1	146	110
		(B) I	45	23.7	7.43	98.1	3.9	--	--
		II	30	21.1	7.61	98.9	4.1	--	--
		III	43	24.0	7.48	98.8	--	--	--

* I indicates control; II, hyperventilation with room air; III, hyperventilation with 6% CO_2.
† $PaCO_2$ indicates arterial blood CO_2 tension (mm. Hg).
‡ $CaCO_2$ indicates arterial blood CO_2 content (mM/L.).
§ Sao_2 indicates arterial blood oxygen saturation (%).

intravenous injection of 20μg. of epinephrine in Patient 12 is illustrated in Figure 9. No alteration of blood pH was observed.

In two of four patients, intravenous phentolamine prevented the changes in the electrocardiogram during hyperventilation as well as during the administration of epinephrine (Fig. 10). In two of three patients, the change in the T-wave during hyperventilation was less conspicuous about

TABLE 3.—*Serum Calcium and Glutamic Oxalacetic Transaminase in Patients with the Hyperventilation Syndrome*

Patient	Periods of Study *	Calcium, Mg. %		SGOT, Units
		Total	Ultrafiltrable	
12	I	10.6	6.8	25
	II	10.0	6.6	25
	III	10.0	6.7	50
13	I	11.2 (?)	5.9	25
	II	10.1	5.8	25
	III	10.1	5.8	25
14	I	9.9	5.9	18
	II	10.2	5.9	22
	III	10.1	6.2	18
15	I	10.2	5.6	--
	II	10.3	5.5	--
	III	10.2	5.5	--
18	I	10.5	--	25
	II	10.0	--	25
	III	9.7	--	25
2	I	--	--	12
	II	--	--	12
	III	--	--	16

* I indicates control; II, hyperventilation with room air; III, hyperventilation with 6% CO_2.
† SGOT indicates serum glutamic oxalacetic transaminase.

30 minutes following an intravenous injection of 30 mg. of propantheline. In two patients, sublingual glyceryl trinitrate failed to prevent the T-wave inversion during hyperventilation, although intravenous potassium blocked the change (Fig. 11).

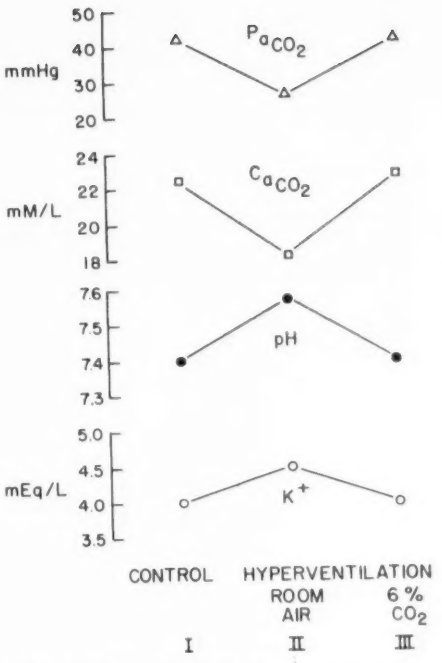


Fig. 6.—Mean values of arterial CO_2 tension, CO_2 content, pH, and serum potassium from 18 patients during periods of control, hyperventilation with room air, and hyperventilation with 6% CO_2.

In four of eight patients, electrocardiographic changes were observed during exercise which resembled those occurring

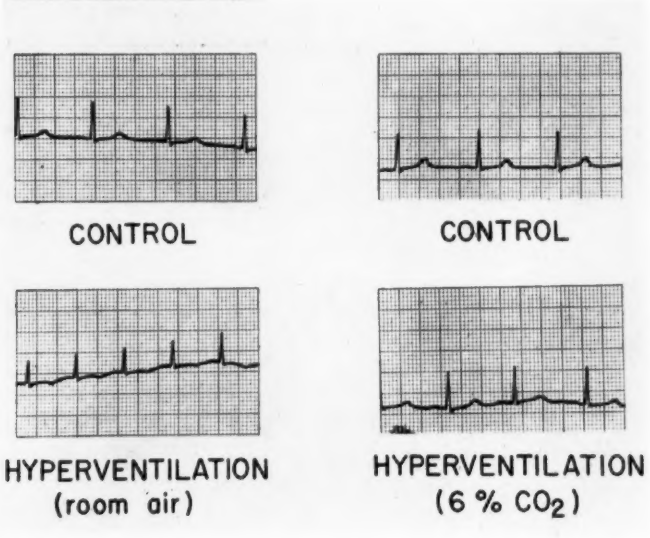


Fig. 7.—Electrocardiographic tracings recorded during hyperventilation with room air and with 6% CO_2 in Patient 21, a 37-year-old woman. Note the absence of inversion of T-waves during hyperventilation with 6% CO_2.

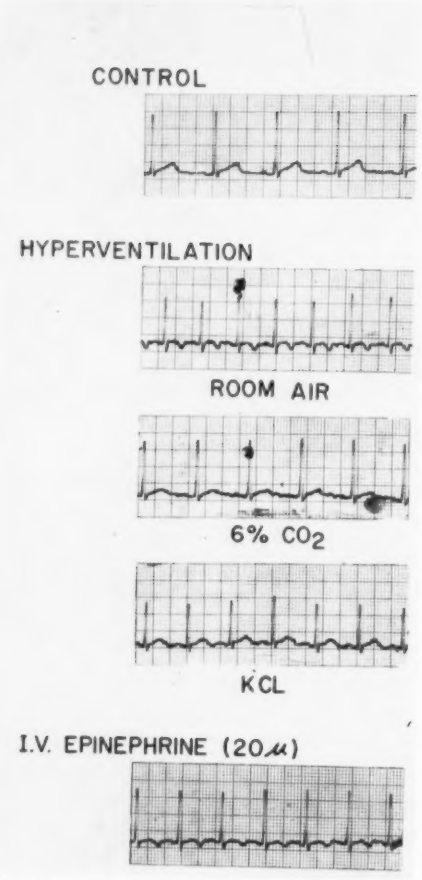


Fig. 8.—Electrocardiogram of Patient 18, a 27-year-old man, showing inversion of T-waves during hyperventilation with room air as well as following intravenous epinephrine. The T-wave change was prevented by either hyperventilation with 6% CO_2 or intravenous administration of potassium chloride.

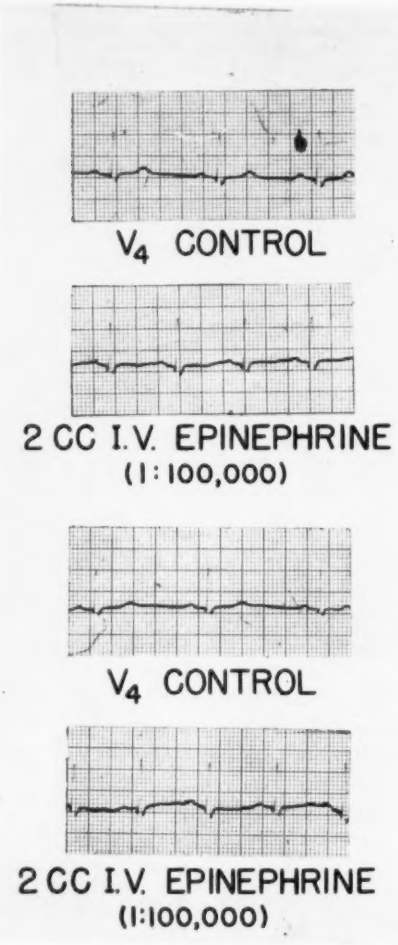


Fig. 9.—Reproducible change with T-wave of Patient 12, a 39-year-old woman, on two separate occasions during intravenous infusion of 20μg. of epinephrine.

during hyperventilation (Fig. 12). In the remaining four patients, the T-wave was inverted during hyperventilation but no significant change occurred during exercise.

Comment

The hyperventilation syndrome not uncommonly occurs in patients who are anxious and emotionally unstable. Its clinical characteristics have been summarized recently by Singer,[23] who found an incidence of 6.3% among 800 female military dependents. Rice[4] found the syndrome in 10.7% of 1,000 ambulatory patients. In our clinic, 6% of new patients referred for cardiac evaluation were considered to have had symptoms diagnostic or highly suggestive of this syndrome. It was more frequent among women.

All of our patients complained of sharp pain, discomfort, or heaviness, which was usually precordial and had no definite relation to exertion. In several patients, the pain was relieved by glyceryl trinitrate.

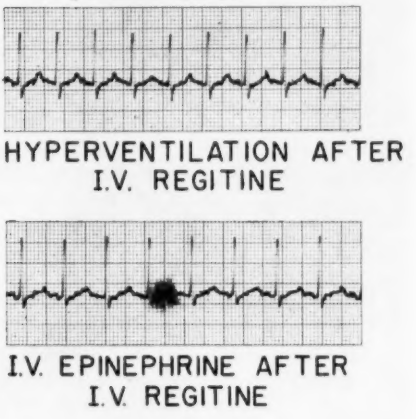


Fig. 10.—Electrocardiogram of Patient 18, a 27-year-old man, showing the effect of intravenous phentolamine (Regitine), which prevents T-wave inversion during hyperventilation and following epinephrine administration. Compare the changes shown in Figure 8.

The cause of the pain is unknown, but it may be due to spasm of the intercostal, pectoral, or diaphragmatic muscles during respiratory alkalosis. Breathlessness or "exertional dyspnea" was the next most frequent symptom, usually accentuated by tension and anxiety. About one-third of patients complained of fatigue, "nervousness," and palpitation.

Apprehension may cause these patients to hyperventilate during the application of electrodes and during the recording of an electrocardiogram. Hence, it is not unusual to observe abnormalities in the routine electrocardiograms. For example, a tracing obtained from Patient 18 immediately after cessation of a period of voluntary hyperventilation exhibited an abnormality almost identical to that observed in a routine electrocardiogram taken in the referring physician's office (Fig. 2*C*).

The electrocardiographic abnormalities during hyperventilation were reproducible in each patient. They appeared as early as 15 seconds after the beginning of hyperventilation and, in most instances, returned to normal within about 1 minute after cessation of hyperventilation.

The mechanism of the electrocardiographic changes during hyperventilation is obscure. Although the heart rate was consistently more rapid during hyperventilation with room air than with 6% CO_2, tachycardia alone was not important, for as few or no changes were observed in the

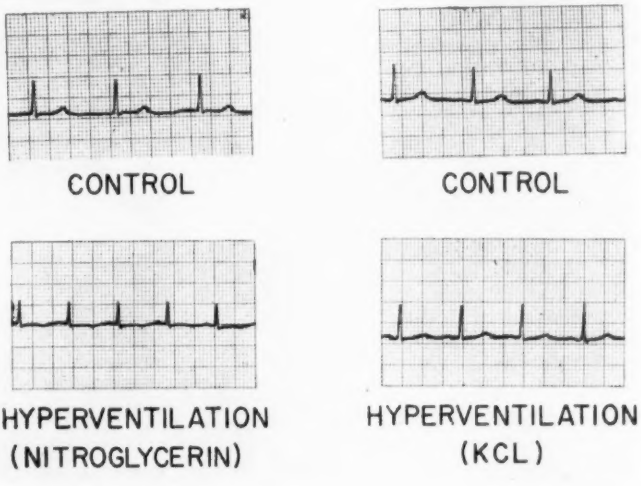


Fig. 11.—Electrocardiogram of Patient 21, a 37-year-old woman, showing the failure of glyceryl trinitrate (nitroglycerin) and the success of potassium chloride in preventing inversion of T-waves during hyperventilation.

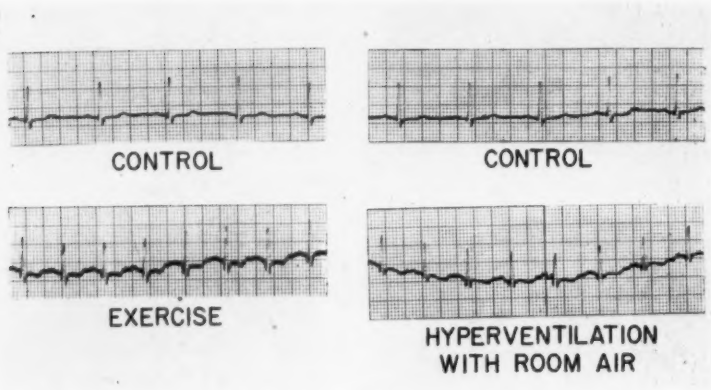


Fig. 12.—Electrocardiogram of Patient 12, a 39-year-old woman, recorded during exercise compared with that during hyperventilation. Note the similarity of the changes in the T-wave.

electrocardiogram of patients who experienced tachycardia following intravenous propantheline. Myocardial hypoxia or constriction of coronary arteries was probably not responsible for the T-wave changes, because the abnormalities were not altered by either inhalation of 100% O_2 or by the sublingual administration of glyceryl trinitrate. This was in agreement with the observations made by Christensen.[15]

A tentative explanation is offered based upon present observations. Hyperventilation precipitates at least two series of events: (1) respiratory alkalosis and (2) probable autonomic stimulation (Fig. 13). With the production of respiratory alkalosis, an exchange of ions occurs across cell membranes. As the pH of the blood rises, it is suggested that potassium leaves the cells, accounting for the temporary rise in serum potassium concentration.

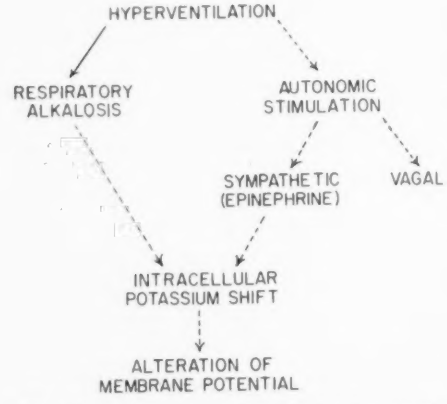


Fig. 13.—A tentative explanation for the possible mechanisms of the electrocardiographic changes observed during hyperventilation. The interrupted lines indicate hypothetical pathways.

It is possible that hyperventilation may augment the secretion of epinephrine, resulting in heightened sympathetic tone. The possibility of autonomic stimulation was mentioned by Kerr and his associates in 1937.[1] It has been shown in animals [24,25] and in man [26] that a transient rise in serum potassium concentration occurs following epinephrine injection, the probable source being intracellular potassium. A larger proportion of the potassium released is probably derived from hepatic cells,[24,25] although the contribution by the myocardial cells has not been extensively investigated.

With a disturbance of the intracellular concentration of potassium, alteration of potential across the myocardial cell membrane might be expected. It is not clear why such changes should occur primarily in tense, anxious, or emotionally unstable persons. A possible direct effect of epinephrine on the electrical activity of the myocardial cells has been postulated in these patients.[27] In our series of normal controls, neither hyperventilation nor intravenous epinephrine produced any significant change in the electrocardiogram.

The electrocardiographic changes were prevented by counteracting either the respiratory alkalosis (hyperventilation with CO_2) or, in some instances, circulating epinephrine (intravenous phentolamine). Barach and his associates [28] have shown that electrocardiographic changes resulting from inhalation of 10%-12% O_2 mixture may be prevented by addition of 2% to 3% CO_2. The effect of the migration of potassium was probably minimized by administration of potassium either intravenously in our cases or orally as reported by Wasserburger.[12,13]

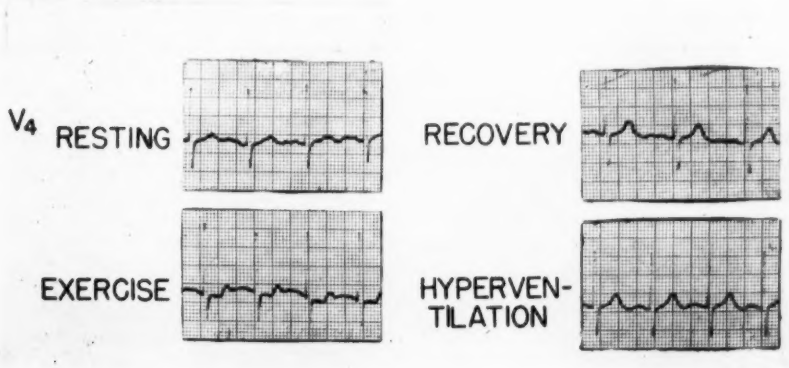
Wasserburger [12,13] thought that hypervagotonia might be important in producing the electrocardiographic abnormality, and he was able to block the changes with intravenous propantheline. Our experience in this regard is limited. In two of three patients, the electrocardiographic changes during hyperventilation were partly blocked by intravenous propantheline.

The identical change in the T-wave observed during exercise and hyperventilation in four of our eight patients is of clinical importance. Inversion of the T-wave is one of the criteria for "coronary insufficiency" in a standard exercise test.[29] In a previous paper [30] we also interpreted inversion of T-wave during exercise as evidence for "coronary insufficiency." From the present studies we now believe that this criterion cannot be applied to all cases. In other words, in patients with anxiety and emotional instability, alteration of the T-wave alone during exercise should not be considered as evidence of "coronary insufficiency" unless the electrocardiogram during hyperventilation has been compared. However, it should be pointed out that the inverted T-wave during hyperventilation was never deeper than 0.4 mv. in our cases. Depression of the ST segment during hyperventilation was much less frequently seen than T-wave inversion in our series. In all cases these changes usually lasted for less than one minute following the cessation of hyperventilation. Therefore, if depression of the ST segment occurs during exercise and persists for several minutes throughout recovery, especially in association with deep inversion of the T-wave, such a change indicates an abnormal response to exertion.

As shown in Figure 14, some patients with coronary artery disease and angina pectoris will demonstrate abnormal electrocardiographic changes with exertion but not with hyperventilation. In these cases, a correct diagnosis is not difficult.

It is important to emphasize that the hyperventilation syndrome may coexist with organic heart disease. Chamberlain, in

Fig. 14.—Electrocardiogram obtained from Patient 10, a 54-year-old man, with coronary artery disease and angina pectoris, showing definite ST depression during exercise but no significant change during voluntary hyperventilation. The ST depression persisted for four minutes after exercise.



discussing Thompson's paper,[6] mentioned that the electrocardiograms of two of his patients were normal at rest but became abnormal with hyperventilation, fitting well into the hyperventilation syndrome. Both patients died suddenly, and postmortem examination showed that death was the result of coronary artery disease. Recently, we have seen three patients with proven coronary artery disease who experienced angina during states of anxiety or emotional disturbance in association with classical symptoms of hyperventilation syndrome. Prompt recognition and proper management of this syndrome in these patients appreciably lessens their symptoms and fear.

Summary and Conclusion

Patients with the hyperventilation syndrome frequently exhibit electrocardiographic abnormalities consisting of inversion of the T-wave and/or, less frequently, depression of the ST segment. These changes may be reproduced by voluntary hyperventilation or intravenous epinephrine. Inhalation of CO_2 or administration of potassium has been shown to prevent these abnormalities. In certain cases, the changes may be blocked by phentolamine (Regitine) or propantheline (Pro-Banthine).

It is suggested that electrocardiographic changes during hyperventilation may be due to the combined effects of respiratory alkalosis and augmented sympathetic tone from secretion of epinephrine, causing a migration of intracellular potassium and alteration of membrane potential across the myocardial-cell membranes.

The hyperventilation syndrome may be mistaken for organic heart disease, particularly when precordial pain is a presenting symptom and a transient change in the T-wave is observed in the electrocardiogram during exercise. Cautious interpretation is required if an erroneous diagnosis of organic heart disease is to be avoided. However, it should be emphasized that hyperventilation syndrome may coexist with organic heart disease and may unnecessarily exaggerate the patient's suffering and fear if unrecognized.

Dr. William B. Mason and his associates determined the electrolytes and glutamic oxalacetic transaminase, and Dr. A. Raymond Terepka analyzed ultrafiltrable calcium.

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Immunological Evaluation of Monovalent Influenza Vaccine in Adults and in Children

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With the Technical Assistance of Florence W. Jensen, B.A., and Lorraine Tauber, M.A.

The characteristic ability of influenza viruses to undergo variation in antigenic structure has given rise to a new family of influenza A strains, now officially referred to as the "Asian family."[1] With the first recognized appearance and isolation of this new virus, early in 1957, and the decision to develop vaccines for active immunization against this new antigenic variant,[2] emphasis was placed anew on problems which required a review of our previous knowledge of the antigenic behavior of Type A influenza viruses as well as of the immunologic response in man when exposed to new variants of the Type A group of viruses.

Early studies on antigenic variants of influenza A viruses showed that protection induced by active immunization was greatest against the homologous virus strain and that the efficacy of immunization against heterologous strains depended upon antigenic relationships between the immunizing and the infecting virus strains.[3] Apparently no completely new antigen has appeared within the influenza A group of viruses, and the antigenic components of strains isolated over a period of years have not yet disappeared.[4] Thus, while the sera of young Americans have been singularly devoid of antibodies against the Asian strain,[1] "older" adults, especially those over 70 years of age, have occasionally been found to possess antibodies against this 1957 strain.[5] (See especially Reference 6.)

Successive experience with the diversity of antigenic components encountered among strains of influenza A virus eventuates in a broadened antibody response; the humoral antibody spectrum engendered by these repeated antigenic experiences constitutes a "recapitulation," readily demonstrable by serologic means, of past infections produced by members of the different families of influenza A viruses, i. e., by variants of the Type A virus.[7] It has been shown that prior infection with antigenic variants of influenza A virus results in an antibody-orienting effect and that the subsequent use of a monovalent vaccine elicits predominantly a "booster" response directed against the antigenic components of the strains with which the person has had previous experience.[7] Consequently, monovalent vaccines prepared from recently isolated strains may call forth only a poor antibody response in young subjects with little prior experience with the antigens of influenza viruses.[8]

It has been shown, with vaccines available prior to the appearance of the Asian strain, that the intradermal route of inoculation is effective in the production of antibodies.[9-11] Recent reports on the use of the Asian strain vaccine by the intradermal route, however, are in conflict, some reports

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indicating that this route can be used effectively,[12,13] others, that it cannot.[14] It has been postulated that the degree of antibody response to the Asian strain virus may be related to the total amount of antigen administered in the vaccine dose used, and hence an increase in the antigenic content of Asian strain vaccine was early proposed.[2]

The purpose of the present investigation was to compare the immunologic response to the new (Asian) strain of influenza A virus in young children, who had had little previous experience with influenza viruses, and in older adults, who might be presumed to have had extensive prior experience. Intradermal and subcutaneous routes of inoculation were used, the dosages administered being those recommended on the basis of experience with influenza vaccines available in the past.

Material and Methods

Vaccine.—The vaccine used was a monovalent, aqueous type of preparation containing the Asian strain, A/Japan/305/57.* This vaccine was stated to contain 1,000 chick-cell-agglutination (CCA) units per milliliter of solution; for use it was diluted with isotonic salt solution to give a virus concentration of 200 CCA units per milliliter. (A small experiment was also conducted with vaccine diluted to contain 400 CCA units per milliliter.) The various dosages that were utilized during the course of the study are indicated as the findings are presented.

Study Population.—The adult subjects were all inhabitants of a home for the aged† in San Francisco; the children were all from the community of Berkeley, Calif., and were under the supervision of a group of pediatricians in that city. No subject, child or adult, with a history of a recent febrile illness was accepted into the investigation. If any febrile illness occurred in the family of any child during the interval which elapsed between the first inoculation of vaccine and the last bleeding, the child was eliminated from the series. Any febrile illness in the adult volunteers during this interval of time was also reason for rejection from the investigation. No abnormal incidence of respiratory tract infection was noted in the home for the aged during the period of investigation, and it was assumed that the intimate contact among these persons would result in many clinical cases of influenza if the virus were present.

Laboratory Examinations.—In order to study the humoral antibody response to vaccination, blood specimens were taken prior to injection with vaccine; two weeks later, preceding the second inoculation, when this was given, and two weeks after the second inoculation.

Hemagglutination-inhibiting (H-I) and complement-fixing (C-F) antibody titers were determined by the standard methods of the Viral and Rickettsial Disease Laboratory of the California State Department of Public Health, which are described in a recent compend of diagnostic procedures for virus and rickettsial diseases.[15]

Nonspecific inhibitors of hemagglutination were destroyed by treatment of the serum specimens with potassium periodate, and the 10th passage level of the egg-ferret-mouse-egg passage strain of the A/Japan/305/57 virus was used as the test antigen. The final concentration of virus in the hemagglutination inhibition test was 4 CCA units. The H-I antibody titer was recorded as the highest dilution of serum which completely inhibited agglutination. All titers, both H-I and C-F, are expressed as the reciprocal of the initial serum dilution (*not* of the final dilution).

Since the complement-fixation test does not distinguish between members of the several families within the influenza A group,[16] an influenza A′ virus, known as the A/Be/5/48, or Spirup, strain, was used in the preparation of the complement-fixing antigen (soluble type). This strain has been employed in the laboratory of one of us (E. H. L.) for many years as the standard source for complement-fixing antigen for the influenza A group of viruses.

Presentation of Data.—In the several tables and in the discussion antibody levels are presented as reciprocals of serum dilutions or as geometric means of the titer. Wherever the term "mean" is used or implied, the geometric mean is understood. In order to calculate this mean, we assigned an arbitrary titer to sera which contained no demonstrable antibody by the methods used. Thus, in the hemagglutination-inhibition test the lowest serum dilution employed was 1:4; consequently all titers of $<1:4$ were considered to be 1:2 for computational purposes. Furthermore, the highest dilution used was 1:2,048, and all titers greater than this were recorded as 1:2,048.

In the complement-fixation test, the lowest serum dilution used was 1:8, and all titers of less than this were considered to be 1:4 for computation of the geometric mean.

*This vaccine was provided by the Lederle Laboratories Division, American Cyanamid Company, through the courtesy of J. M. Ruegsegger, M.D.

†Laguna Honda Home, H. D. Crall, M.D., Assistant Medical Superintendent.

TABLE 1.—*Age Distribution of Persons Given Inoculations of Monovalent Influenza Vaccine, Asian Strain*

Age Group, Yr.	Persons, No.
Children	133
1- 5	57
6-10	55
11-15	21
Adults	142
50-60	28
61-70	48
71-80	40
80+	26

Results

The age distribution of the two population groups in whom the antibody response to Asian strain vaccine was studied is presented in Table 1. It will be noted that 66 adults were in the age group over 70 years; persons in this group have been reported [5,6] to possess H-I antibody to the Asian strain virus, presumably [6] but not necessarily [17] acquired during the 1889-1890 epidemic of influenza.

The C-F antibody, unlike the H-I antibody, is group-specific, and its presence, therefore, indicates that the person has had prior experience with influenza virus, irrespective of the family or families of virus which have produced the infection. Absence of demonstrable C-F antibody points to the absence of infection, at least within the relatively recent past. Consequently, it would be expected that only a very small proportion of very young people would possess complement-fixing antibody and that the proportion of persons with such antibody would increase, generally speaking, with age. This is shown in Table 2, which presents the complement-fixing antibody titers of the several age groups prior to vaccination. The discrepancy in the total number of persons, child and adult, listed in Tables 1 and 2 arises from the fact that the sera of eight children and nine adults could not be examined because of their high anticomplementary activity. As shown in Table 2, only 11% of the children, age 1 to 5 years, possessed C-F antibody to influenza A virus but in the 6- to 15-year age group, the proportion of youths with antibody had increased to 28%. In the adult population, C-F antibody was encountered in the majority of persons in all age groups, but in the age group of less than 70 years, 82% had antibody, whereas in the age group of over 70 years the proportion had decreased to 58%.

TABLE 2.—*Distribution of Complement-Fixing Antibody Titers in Children and Adults Prior to Vaccination with Asian Strain Influenza Virus*

Age Group		C-F Antibody Titers, No. Persons		
Yr.	No.	<8	8	>16
Children				
1-5	57	51	4	2
6-15	68	49	6	13
Total	125	100	10	15
Adults				
50-70	73	13	22	38
70+	60	25	12	23
Total	133	38	34	61

Since the H-I antibody has a strongly strain-specific reactivity and since the Asian strain virus represents a new variant of influenza A virus, with which the population, in general, had had virtually no prior experience, it would be expected that the proportion of persons, if any, with H-I antibody to the Asian strain virus would be very low. Indeed, none of the 133 children listed in Table 1 had any demonstrable H-I antibody against the Asian strain prior to vaccination. Of the 142 adults, 111 also possessed no demonstrable H-I antibody to this virus strain (Table 3). The 31 adults, representing 22% of the group, who showed

TABLE 3.—*Distribution of Hemagglutination-Inhibiting Antibody Titers to Asian Strain Influenza A Virus Prior to Vaccination in "Older" Adults, 1957*

Age Group		Hemagglutination-Inhibiting Antibody Titers, No. of Persons			
Yr.	No.	<4	4	8	16
50-70	76	61	8	5	2
70+	66	50	5	8	3
Total	142	111	13	13	5

TABLE 4.—*Hemagglutination-Inhibiting Antibody Response in Adults to Intradermal Injection of Asian Strain Influenza Vaccine—Effects of a Single Injection Versus Repeated Injection*

Vaccine		H-I Antibody Response			
Dose, Ml.	CCA Units	Mean Titer Postvac.	Fold Rise in Titer	Persons with Rise, No.	Total Tested
0.1	20	20.16	9.61	10	12
0.1	20 (twice)	35.92	12.97	11	12
0.2	40	13.57	5.19	37	75
0.2	40 (twice)	12.34	4.96	31	43

TABLE 5.—*Hemagglutination-Inhibiting Antibody Response in Children to Intradermal Injection of Asian Strain Influenza Vaccine—Effects of a Single Injection Versus Repeated Injection*

Vaccine		H-I Antibody Response			
Dose, Ml.	CCA Units	Mean Titer Postvac.	Fold Rise in Titer	Persons with Rise, No.	Total Tested
0.1	20	2.08	1.04	1	18
0.1	20 (twice)	7.51	3.76	8	11
0.2	40	2.54	1.27	5	32
0.2	40 (twice)	11.20	5.60	52	60
0.2	80	2.0	0	0	6
0.2	80 (twice)	12.13	6.06	5	5

detectable H-I antibody were scattered throughout all the age groups. Antibody to the Asian strain virus was not encountered primarily in persons who were over 70 years of age and who were exposed to the 1889-1890 epidemic of influenza.

The effect on the antibody response of two intradermal injections of vaccine, as compared with a single injection, is presented in Tables 4 and 5. The volume of inoculum administered was 0.1 ml. or 0.2 ml., and the amount of viral material in terms of CCA units varied as indicated in the two tables.

Table 4 presents the data pertinent to the adult group. The intradermal administration of two doses of vaccine two weeks apart did not possess any marked advantage over a single dose since, although proportionately more persons showed a rise in H-I antibody titer after the second injection, there was no significant difference in the geometric mean antibody titer of the group as a whole after vaccination. It will be noted that in the group of persons who received only 0.1 ml. of vaccine intradermally there appeared to be some advantage to two injections, since the mean antibody titer in this small group was higher than in the group which had received only one injection. However, statistical analysis of this series of subjects showed that the 99% confidence intervals of the medians of the titers obtained after one inoculation of vaccine and of the medians of the titers obtained after two inoculations overlapped, and, therefore, the two medians cannot be considered as significantly different.[18] Likewise, similar statistical comparisons between the 0.1 ml. and the 0.2 ml. dosages show that the confidence intervals between these groups also overlap, and so no significant difference in the population medians can be considered to exist. It thus appears that not only was there no significant advantage to repetition of the intradermal dosages in the adult group but also, despite the paradoxical higher mean in the postvaccination titers obtained with the 0.1 ml. dosage, there was no significant difference between the two dosages employed.

Table 5 shows that repetition of the intradermal injection of vaccine in children produced notably different results in comparison to those observed in adults. First, neither the volume (0.1 or 0.2 ml.) nor the concentration of antigen (20, 40, or 80 CCA units) administered on a single occasion produced any change in the antibody titer, when it is considered that the geometric mean of the prevaccination titer was 2.0 (based on the assumption that all antibody titers of $<1:4$ were 1:2). In addition, the mean fold rise in H-I antibody titer from a single injection of 0.1 or 0.2 ml., regardless of the antigenic mass, was only slightly greater than unity. In sharp

contrast, two injections of either 0.1 ml. or 0.2 ml., given two weeks apart, produced a mean fold increase in titer of substantial proportions and comparable to the increases obtained in adults after a single intradermal injection. Although not exactly equal to those seen in the adult group, the means of the postvaccination titers were also significantly elevated. While only 1 child of 18 showed a rise in H-I antibody titer after the injection of 0.1 ml. of vaccine, two injections, of 0.1 ml., produced an antibody rise in 8 of 11 children. This same contrast in the antibody levels elicited by single or multiple injections of vaccine is apparent in the group of children who received 0.2 ml. dosages.

Table 5 also presents data on a third group of children, which, while the group was numerically small, are of some interest. The six children in this group received 0.2 ml. of vaccine intradermally, diluted to contain 400 CCA units per milliliter. A single injection of this more concentrated vaccine failed to produce a demonstrable rise in H-I antibody titer. Five of the children received a second dosage of vaccine two weeks after the first, and it will be noted from Table 5 that all five showed a rise in antibody titer, that the mean titer after vaccination was substantially elevated, and that the mean fold rise was comparable to that produced by 0.2 ml. of the more dilute vaccine. Despite the very small size of this group, it would appear that in the child antigenic mass is of less importance than repetition of the dosage in the stimulation of an antibody response by influenzal vaccines. In essence, therefore, all three dosages which were used (shown in Table 5) support the observation that two intradermal injections are required to elicit a good antibody response in the child with no prior experience with the antigens which make up the virus strain(s) in the vaccine.

Table 6 shows the antibody response produced in adults by subcutaneous and by intradermal inoculation of vaccine. A vaccine dose of 1.0 ml. subcutaneously produced a sevenfold rise in titer in 25 of 34 persons, as compared to about four and one-half-fold rise in a similar proportion of persons who received the 0.5 ml. dose; the mean postvaccination titer was also slightly higher in the former group. These data suggest that antigenic mass is of importance in the adult and are thus in agreement with recent observations on this aspect.[13] However, the findings presented in Table 4 indicate that an increase in the antigenic content of vaccine administered intradermally does not significantly increase the resultant postvaccination titers and that there is no obvious advantage to repetition of the dosage in adults. In Table 6, therefore, the results obtained with a single subcutaneous inoculation are compared with results obtained with a single intradermal injection (data from Table 4). It will be noted that, with the exception of the small group which received the 0.1 ml. dosage, the mean postvaccination titers and the mean fold increases are comparable in the three groups which received amounts of antigen varying from 40 CCA units to 200 CCA units. It will be recalled that, in comparing the 0.1 ml. dosage group with the 0.2 ml. dosage group in connection with Table 4, the disparity between the postvaccination titers and the mean fold increases between these two groups was shown to be statistically not significant because of the small size of the 0.1 ml. dosage group. Consequently, it would seem that while an increase in the amount of antigen given subcutaneously may offer

TABLE 6.—*Comparison of Hemagglutination-Inhibiting Antibody Response Elicited in Adults by Subcutaneous and by Intradermal Injection of Vaccine*

Vaccine			H-I Antibody Response			
Dose, Ml.	CCA Units	Route	Mean Titer Postvac.	Fold Rise in Titer	Persons with Rise, No.	Total Tested
0.5	100	SC	11.52	4.46	13	19
1.0	200	SC	15.36	6.8	25	34
0.1	20	ID	20.16	9.61	10	12
0.2	40	ID	13.57	5.19	37	75

TABLE 7.—*Comparison of Hemagglutination-Inhibiting Antibody Response Produced in Children by Single Subcutaneous Injection and by Two Intradermal Injections of Vaccine*

Vaccine			H-I Antibody Response			
Dose, Ml.	CCA Units	Route	Mean Titer Postvac.	Fold Rise in Titer	Persons with Rise, No.	Total Tested
0.25	50	SC	2.48	1.24	3	13
0.5	100	SC	3.25	1.62	5	20
1.0	200	SC	3.43	1.72	4	9
0.1	20 (twice)	ID	7.51	3.76	8	11
0.2	40 (twice)	ID	11.20	5.60	52	60

some slight advantage in terms of an increased postvaccination titer, i. e., a better antibody response, comparable antibody levels can be achieved with considerably smaller amounts of antigen administered intradermally.

The antibody response elicited by subcutaneous and by intradermal injection of vaccine was also investigated in children, and the data are presented in Table 7. The children who received subcutaneous injections were divided into three groups, which received 0.25 ml., 0.5 ml., and 1.0 ml. of vaccine, representing 50, 100, and 200 CCA units of virus. It will be noted that the antibody response in all three groups was rather poor; the geometric mean of the H-I antibody titers after vaccination was very low in all groups, and there was less than a twofold rise in titer. Some data on the antibody response to intradermal inoculation, presented earlier in Table 5, are included in Table 7 for comparative purposes, and it is readily apparent that the antibody response elicited by two intradermal injections is notably better than that produced by a single subcutaneous injection. Although the total antigenic mass injected by the two routes in some cases was similar, the results of the repeated intradermal inoculation were nevertheless superior—for example, the 0.1 ml. dosage intradermally versus the 0.25 ml. dosage subcutaneously and the 0.2 ml. dosage intradermally versus the 0.5 ml. dosage subcutaneously. However, even two intradermal injections of one-fifth as much antigen were superior to a single large injection subcutaneously, as is shown by comparison of the mean titers and fold rises obtained with 0.1 ml. given intradermally on two occasions with 1.0 ml. given as a single subcutaneous injection.

It is very possible, and probable, that repeated subcutaneous injections of vaccine might have produced antibody responses similar to those elicited by two intradermal injections. Unfortunately, it was not feasible to investigate this possibility because of the reactions to subcutaneously administered materials; 8 of the 42 children given inoculations subcutaneously developed generalized reactions with fever during the evening of the day of inoculation, whereas none of the persons who received vaccine intradermally complained of any untoward reaction.

The extent of the H-I antibody responses elicited by the vaccine in children and in adults is summarized in Table 8 in terms of fold rises in titer. It will be noted that no child under 5 years of age had a thirty-two-fold, or greater, rise in H-I antibody titer while some of the children between the ages of 6 and 15 years and a substantial number of adults had such rises. The age group over 70 showed a greater proportion of such persons than did the age group under 70, no matter which route of inoculation was used. It would seem likely that rises in titer of such magnitude are evidence of previous sensitizing experience with influenza A viruses related to the Asian family and that older age groups would thus have a greater proportion of persons with such experience.

Approximately 20% of the younger children and 15% of the older children showed no rise in antibody titer after two injections of vaccine intradermally, and between 26% and 42% of the adult groups similarly failed to respond with antibody, irrespective of the route of inoculation. (Since, as shown in Table 4, there was no significant

TABLE 8.—*Influence of Age and Route of Inoculation on Hemagglutination-Inhibiting Antibody Response to Asian Strain Influenza Vaccine*

Age Group		Vaccination		Persons with Rise in Titer, %			
Yr.	No.	Route	Injections, No.	0	2-4-Fold	8-16-Fold	32-Fold or More
Children							
1-5	34	ID	2	19.7	32.8	47.1	0
6-15	27	ID	2	14.8	44.4	25.9	14.8
Adults							
50-70	50	ID	1	42.0	24.2	24.0	9.2
Over 70	39	ID	1	25.6	24.3	19.6	30.3
50-70	26	SC	1	34.6	26.9	26.9	11.5
Over 70	27	SC	1	25.9	18.5	30.0	26.2

difference between the results of one and two injections in the adults, only the results of a single intradermal injection are presented for comparative purposes in Table 8.)

Comment

Strains of influenza A virus can be characterized and separated into several categories according to the specific antigenic components present. In 1938, Smith and Andrewes [3] showed, by means of cross neutralization analyses, that there were at least four major antigenic components present among the 28 different strains they studied and that protection conferred by active immunization was greatest against the homologous strain, the efficiency of vaccination against heterologous strains depending upon antigenic relationships. In 1953, Jensen and Francis [4] showed that at least 18 different antigenic components occurred among Type A influenza viruses and that these components were widely shared by various strains. They concluded that up to the time of their study no completely new antigens had appeared in the influenza A group and that the antigenic components of strains that had been isolated over a period of years had not yet disappeared.

Davenport, Hennessy, and Francis [19] studied the level of antibody to various strains of influenza A and B viruses in different age groups and concluded that the antibody spectrum is narrow in the early years of life and becomes broader with age. They also noted that there was a correlation between the period of prevalence of certain strains of influenza virus and the age of the person in whom antibodies to these strains (families) were detectable. From their observations that successive experience with various influenzal antigens results in a broader antibody base, these authors introduced the concept of "serologic recapitulation" of past infection, i. e., infection with strains belonging to a major group or family of influenza viruses leaves a serologic imprint of the family to which the infecting strain belongs. The antibody-orienting effect of prior infection was demonstrated by Davenport and Hennessy [7] by means of the injection of monovalent vaccine which produced a "booster" type of antibody response; the antibody elicited was directed against the antigenic components of the strains with which the person had had prior experience.

Only a few of the adults studied by us possessed demonstrable H-I antibody to the Asian strain, but the antibody response of the group as a whole to the monovalent vaccine containing this strain was such as to indicate that members of the group had had prior experience with this or related strains, regardless of the absence of detectable levels of antibody in their prevaccination blood specimens. In these "older" adults with extensive experience to influenza A virus, a single inoculation of the Asian strain was sufficient to raise their antibody levels to appreciable heights. The antibody response to the inoculum resem-

bled a "booster" effect and probably constitutes more significant evidence of prior experience with related influenzal antigens than does the presence or absence of detectable H-I antibodies in the serum prior to vaccination.

The complete absence of demonstrable H-I antibody to the Asian strain and the relative absence of C-F antibody to influenza viruses of Type A (Table 2) indicate that the children, as a group, had had far less influenza experience than the adults. In these children the antibody response to a single injection of the monovalent Asian strain vaccine was very poor, but when the injection was repeated a very good response was elicited. The two injections might thus be considered as "sensitizing" and "booster" doses.

Quilligan and co-workers[20] showed that repeated subcutaneous injections of Type A influenza virus (PR8 strain) called forth a better antibody response in children than did a single injection and found that children over the age of 4 years had a better antibody response to a single injection of the viral antigen than did younger children. These investigators were able to relate the better antibody response in the older children to prior experience with the influenzal antigen, acquired by virtue of exposure to a recent outbreak of influenza. Davenport and Hennessy,[7] as mentioned earlier, also concluded that the response of a person to a monovalent influenza vaccine is predominantly "booster" in type, serving to recall antibody against a major antigen with which the person has had experience in the past.

The importance of a second inoculation of vaccine in the young age groups is most clearly brought out whenever a "new" strain of influenza virus appears, i. e., a strain whose antigenic structure is not closely related to the epidemic strains of recent years. Bruyn, Meiklejohn, and Brainerd[11] found that a single intradermal or subcutaneous injection of a monovalent vaccine containing the PR8 strain of influenza A virus produced satisfactory antibody levels in young adults. These results, obtained in investigations conducted shortly after the appearance of the FM-1, or A′, family of viruses indicated that the children involved had, despite their youth, experienced exposure to a strain of influenza virus closely related to the PR8 strain. Meiklejohn and associates,[8] in comparisons of monovalent vaccines containing representatives of the A and A′ families (A/PR8/1934 and A/FM-1/1947, respectively), found that the antibody response to a single subcutaneous injection of the more recent, i. e., FM-1, strain was considerably less than that of the older strain, i. e., PR8. It might now be postulated that this poor antibody response in the young adults studied was referable to their lack of previous experience with the antigens present in the newer virus. A second injection of the vaccine containing the FM-1 (newer) strain might also have produced a "booster" effect and a satisfactory antibody response. With respect to the newest family of viruses to appear on the scene, the Asian strain family, Hilleman and associates[13] have also presented data showing that a second injection, subcutaneous or intradermal, of a monovalent Asian strain vaccine produces a more satisfactory antibody response than does a single injection.

The advantages of the intradermal route of inoculation include not only a reduction in the incidence of systemic reactions to the vaccine[10,11] but also a factor of safety in its use in persons who are potentially allergic to egg materials. In the present investigation, as well as in earlier studies,[9,10] the vaccine was given by this route with no untoward reactions to persons who had experienced a variety of manifestations of allergy to egg proteins. It seems likely, however, that the content of egg protein in an intradermal inoculum of 0.1 or 0.2 ml. of influenza vaccine is entirely comparable to the content of egg proteins in the allergy-testing materials that are used with impunity in such sensitive persons.

The study reported here suggests that the total antigenic mass of the vaccine inoculum is of less importance in eliciting an antibody response in the younger age group than is repetition of the inoculation. This opinion is supported by the studies of Hilleman et al.[13] The increase in H-I antibody titer obtained by these investigators after intradermal injection of 62.5 CCA units of Asian vaccine was comparable to the increases observed by us after the injection of as little as 20 CCA units of Asian strain vaccine. In addition, these authors found increases in titer comparable to those observed by us to follow the inoculation of considerably greater amounts of antigen. Since reactions to influenza vaccine are related to the content of influenza virus[21] there appears to be little advantage to increasing the antigenic content of the vaccine if the same end-result can be obtained by repetition of inoculation of a more dilute vaccine preparation.

While a study of reactions to the Asian strain vaccine was not a part of the present investigation, the incidence of such reactions was very small in all groups. Sadusk and Nesche,[22] in a study of reactions to influenza vaccines administered subcutaneously, reported the incidence of systemic reactions to be about 3.6% in men and 8.8% in women. They observed that this reaction rate, associated with a vaccine containing 200 CCA units of Asian strain virus, was considerably lower than that associated with the polyvalent vaccine which was previously available and which contained up to 1,500 CCA units of virus. On the other hand, Hilleman and associates[13] found that reactions attendant upon subcutaneous injection of a monovalent vaccine containing as much as 1,000 CCA units of Asian strain virus were minimal.

Summary

The antibody response of young children and older adults to a monovalent Asian strain vaccine was compared with use of subcutaneous and intradermal routes of inoculation with various amounts of vaccine.

It was found that the extent of the antibody response is conditioned by prior infection with influenza A viruses related, even if distantly, to those in the vaccine or by prior immunologic exposure, through vaccination, to the antigens present in that vaccine.

In the adult, a single injection of vaccine intradermally or subcutaneously produced a significant antibody response.

In the child, repeated injection of vaccine rather than increased antigenic mass was required to elicit significant antibody response. This presumably reflects lack of prior experience with the antigens of influenza A viruses.

Repetition of inoculation appears to be as important in the adult as in the "immunologically inexperienced" child whenever variation in influenza A virus results in the appearance of a new "family" of strains with which the population has had little (or no) prior experience.

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Radioiodine Therapy of Hyperthyroidism

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Between September, 1945, and June, 1957, four hundred thirty-one patients with hyperthyroidism were treated with radioiodine at the University of California Medical Center. Although other large series of radioiodine-treated patients have been recorded,[1-3] certain features regarding patient selection, duration of follow-up of the initial group of patients, incidence and time of hypothyroidism, and effect on exophthalmos suggested the present analysis.

All patients with hyperthyroidism in whom definitive therapy with radioiodine was initiated between September, 1945, and June, 1957, are included in this study. Although at first patients with nodular goiter were not treated, after November, 1948, these have been accepted if a reasonably strong contraindication to thyroidectomy was present. Previous to 1953, patients of all ages were treated; patients under 40 years of age were treated since that time, however, only if there was a postsurgical recurrence or some factor contraindicating surgery or other form of therapy. Pregnancy or the presence of a single nodule has always been considered an absolute contraindication to radioiodine therapy.

All patients had convincing evidence of hyperthyroidism at the time radioiodine therapy was instituted. The diagnosis was based on symptoms, physical findings, basal metabolic rate, fasting serum protein-bound iodine (PBI), serum cholesterol, and thyroid uptake of radioiodine. Not all diagnostic studies were performed on each patient. In general, the fasting PBI and thyroid radioiodine-uptake studies proved the most helpful laboratory aids.

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Many of these patients have been followed jointly with members of other departments, particularly the Thyroid Clinic, which during recent years has been headed by Mayo Soley, Morris Dailey, and Bernhard Anderson. Other patients have been referred directly to the Radioiodine Unit and have been handled primarily by members of the unit. All radioiodine therapy has been administered in the Radioiodine Unit and has been under our supervision. The early results of treatment in the first 100 patients have been described.[4]

The age distribution of the patients, according to goiter type, is given in Table 1. Including 3 with postsurgical recurrence of thyrotoxicosis, there were 20 patients between 2 and 20 years of age at the time of therapy; these were all females. Eighteen of the patients under age 20 were treated prior to July, 1953; sixteen of these had toxic diffuse goiters without previous surgical therapy, and two had postsurgical recurrence. A total of 324 patients had hyperthyroidism with either diffusely enlarged or normal-sized thyroids. Those in whom the thyroid was of normal size were relatively few in number, and, since their clinical behavior and response to therapy

TABLE 1.—*Age Distribution of the 431 Patients Treated with Radioiodine for Thyrotoxicosis*

Age, Yr.	Type of Toxic Goiter		
	Diffuse *	Postsurgical Recurrence	Nodular
0-9	5	0	0
10-19	12	3	0
20-29	55	13	0
30-39	83	17	0
>40	169	45	29
Total	324	78	29

* Includes those with normal-sized thyroids.

were essentially the same as of patients with diffusely enlarged goiter, these groups were classified together. Seventy-eight patients had thyrotoxicosis recurrent after subtotal thyroidectomy. Many of the postsurgical thyroids were lobular and asymmetrically enlarged, but none of these was classified with the toxic nodular goiters. Although thyroidectomy was considered the treatment of preference in patients with toxic nodular goiter, 29 patients with this type of goiter were treated with I^{131} either because of refusal of or medical contraindication to surgery. A number of patients in each category, particularly in the toxic diffuse goiter group, had had some previous therapy with one of the antithyroid drugs. By current standards many of these had received inadequate drug therapy. In nearly all, either no antithyroid therapy had been given or therapy had been discontinued for several weeks or months before the institution of radioiodine therapy. Patients of all ages appear in the toxic diffuse and postsurgical recurrent goiter groups. However, all patients with toxic nodular goiters were 40 years of age or older.

Two patients inadvertently received therapeutic doses of radioiodine while pregnant. A third patient became pregnant while it was being debated whether or not she was controlled. One of the patients treated while pregnant was a 16-year-old unwed girl, who was given 3.8 mc. of I^{131} at about the sixth month of pregnancy. The infant of this mother was observed for approximately one year after birth, at which time no evidence of thyroid dysfunction or of other abnormality had appeared. At one year this infant was adopted, and further follow-up was not permitted. The second radioiodine-treated mother was 33 years of age and was given her second I^{131} treatment, consisting of 5 mc., at approximately the third week of pregnancy. This patient subsequently delivered a normal infant and, since the thyrotoxicosis had not been completely controlled by the radioiodine, eventually received a subtotal thyroidectomy.

Methods and Therapy

The first seven patients were treated with multiple small doses of I^{131} administered at short intervals. The dose was usually 0.5 mc. of I^{131}, given weekly until evidence appeared of control of the hyperthyroidism.

In the majority of the first 100 patients, an attempt was made to deliver 3,000 to 6,000 β rep to the thyroid at each treatment.[5] According to this plan, patients were re-treated at intervals of about two months until the hyperthyroidism was controlled. This method was cumbersome and costly in that it necessitated a determination of the effective half-life of radioiodine in the thyroid. When in September, 1950, it was observed that few patients receiving under 0.12 mc. per estimated gram of thyroid tissue became hypothyroid and that the majority of the patients required at least this large a dose for control, this plan was abandoned. Thereafter, nearly all patients with diffuse or postsurgical recurrent goiter were given 0.12 mc. of I^{131} per estimated gram of thyroid tissue. In general, successive doses tended to become smaller only as the estimated size of the thyroid decreased. As it became evident that the toxic nodular goiter is more refractory to radioiodine, the dose per estimated gram in these patients was increased. At the present time the initial treatment dose per gram in the patient with a toxic nodular goiter is two to four times the 0.12 mc. per gram given to the patient with a toxic diffuse goiter. Similarly, patients with toxic diffuse goiter who have shown little response to the first or second treatment are now given increased doses at succeeding treatments.

Patients were placed on sedation, dietary regimen, vitamin supplementation, and other supportive therapy as necessary and were seen at monthly intervals. Except for the first few patients, they were re-treated at intervals of approximately two months until hyperthyroidism was controlled. Nearly all were treated as ambulatory patients. A few patients with severe heart disease or other complications were placed on bed rest for the first portion of the therapy. In only two or three very toxic patients was the therapy complicated by the use of antithyroid drugs in addition to radioiodine.

As experience accumulated, it was seen that after a therapeutic dose of I^{131}, alteration of the thyroid uptake curve often preceded changes in the serum PBI level and the clinical status of the patient by several days or weeks. For example, if at two months the uptake curve was in the normal or hypothyroid range and the PBI still elevated, the PBI usually decreased further without additional I^{131} therapy. Regardless of how high the PBI or how toxic the patient, some with a hypothyroid type of uptake curve at two months proceeded to hypothyroidism even though no more I^{131} was given.

Only rarely did a patient with a hypothyroid curve again become toxic. If the uptake curve remained in the hyperthyroid range at two months, further radioiodine therapy was almost invariably required. Future events were not as predictable in cases when the uptake curve at two months indicated normal or elevated iodide trapping with blocked organification. If at two months the thyroid status was not clear, the patient was restudied after an additional three to six weeks.

Except for a few patients lost to follow-up, all were examined and treated periodically until the thyroid function was thought to be normal and stable. Follow-up periods varied from a few months to 13 years. The majority was followed one year or longer. As of June, 1957, all but 16 of the first 175 consecutive patients were still under observation, with observation periods ranging from 5 to 12 years.

During the first 10 years that radioiodine was used, patients who became hypothyroid were not given replacement therapy for several months, in the hope that hypothyroidism would provide stimulus for recovery of thyroid function. Such spontaneous recovery did occur in a few patients. At present, however, a patient is placed on desiccated thyroid as soon as the diagnosis of hypothyroidism is established. That return of thyroid function may occur while the patient is receiving exogenous thyroid substance is illustrated by the fact that recently two patients on desiccated thyroid for four and six months for post radioiodine hypothyroidism showed recovery of thyroid function; one of these patients recovered sufficient function that further replacement therapy was no longer needed, and the other returned to a hyperthyroid level, necessitating re-treatment with I^{131}.

In this analysis, a patient has been classified as hypothyroid if the thyroid function became sufficiently low that it was thought that the patient would be improved by thyroid replacement therapy. Some of these patients were borderline cases and were not unequivocally hypothyroid. The incidence of hypothyroidism would be reduced by a more strict definition. After radioiodine therapy, hyperthyroidism is considered to have recurred if there was an interval of six months or longer between therapy doses. In some, this interval more truly represents a period of indecision, during which the status of the patient was not entirely certain. For this reason some of the so-called recurrences might better have been classed as cases of mild persistence. If these were so reclassified, the apparent rate of recurrence would drop and the number of patients requiring many months for control would increase. Actually this group is small, since a total of only 11 patients was classified as having had a recurrence.

Results and Comment

The hyperthyroidism was definitely controlled in 408, or 95%, of the 431 patients treated. In the 23 (5%) in whom the disease was not known to have been controlled, the treatment was usually incomplete (Table 2). Thirteen of the twenty-three failed to return after one or more treatment doses, and for many of them there is no available evidence as to whether they were controlled. Certainly the nine patients lost during the first two months, i. e., after the initial treatment dose of I^{131}, reflect the transient nature of the population. Impatience of the resident staff led in two patients to propylthiouracil treatment after the initial treatment dose and to a third patient being so treated after the second dose of I^{131}. Two patients became pregnant, and radioiodine therapy was discontinued. In another patient, a thyroid nodule became palpable after the third dose of I^{131} and surgery was performed. One patient showed little if any improvement in

TABLE 2.—*Patients in Whom Hyperthyroidism Was Not Controlled by* I^{131}

Reason for not Completing I^{131} Therapy	Time Followed, Mo.						
	0-2	3-4	5-6	8-10	10-12	12-18	Total
Lost while toxic	9	2	1	1	—	—	13
Placed on propylthiouracil *	2	1	—	—	—	—	3
Became pregnant	0	2	—	—	—	—	2
Nodule(s) became palpable *	—	—	1	—	—	—	1
Too slow *	—	—	—	—	—	1	1
Died while toxic	2	—	—	—	—	1	3
Total	13	5	2	1	0	2	23

* Therapy completed surgically.

TABLE 3.—*Number of Doses of I^{131} to Produce Euthyroidism in Patients with Toxic Goiter*

Type of Goiter	Doses to Euthyroidism, No.								
	1	2	3	4	5	6	7	8	Total
Diffuse	181 (59%)	75	23	15	2	6	4	3	309
Postsurgical recurrence	50 (69%)	16	4	1	2	—	—	—	73
Nodular	11 (42%)	2	5	4	2	1	1	—	26
Total	242 (59%)	93	32	20	6	7	5	3	408

12 months, and subtotal thyroidectomy was done. In this patient, as well as some of the others, the size of the treatment dose should have been increased when it became evident that the dosage schedule was inadequate. Three deaths occurred in patients with uncontrolled hyperthyroidism. The first of these died 17 months after beginning radioiodine therapy, with death being attributed to diabetic acidosis and coma. This patient was only mildly toxic, and, although the radioiodine therapy should have been more aggressive, death was apparently not directly related to either the thyrotoxicity or its treatment. The second death occurred approximately 48 hours after the initial treatment dose in a patient with severe cardiovascular and liver disease. This patient was in congestive failure and had severe jaundice; he apparently died of hepatic failure. The third patient became disoriented two weeks after a single treatment with I^{131} and died one week later. Request for postmortem examination was refused, and the cause of death in this patient was not determined. Although the possibility of thyroid crisis was considered, there was no definite evidence to support this diagnosis. Serum PBI preceding treatment with radioiodine was 18.0μg. %, while at the time of death it was 17.4μg. %.

The remainder of the discussion will be limited to the 408 patients in whom thyrotoxicosis was controlled with radioiodine.

Table 3 shows the number of doses of radioiodine necessary to control hyperthyroidism in the various types of goiter. It is seen that 59% and 69%, respectively, of those with toxic diffuse and postsurgical recurrent goiter were controlled with one treatment, whereas less than one-half of those with nodular goiter were so controlled. From Table 4 it is seen that 45%, 58%, and 27% of patients with toxic diffuse, postsurgical recurrent, and nodular goiter were euthyroid within two months. Since some who were controlled on one dose were not euthyroid before the third month, it is evident that the effect of a single dose of radioiodine cannot always be evaluated within two months. As measured by response to a single dose and by early control, the postsurgical recurrent goiters did slightly better than the diffuse goiters while the nodular glands responded more poorly than either of the other two groups. All patients considered, 59% were controlled

TABLE 4.—*Number of Months to Produce Euthyroidism in Patients with Toxic Goiter*

Type of Goiter	Months to Euthyroidism							
	2	3	4	5-6	7-12	13-17	>18	Total
Diffuse	140 (45%)	48	44	39	29	5	4	309
Postsurgical recurrence	42 (58%)	10	10	3	7	1	—	73
Nodular	7 (27%)	3	2	5	6	2	1	26
Total	189 (46%)	61	56	47	42	8	5	408

TABLE 5.—*Total Dose of I^{131} to Control Hyperthyroidism*

Type of Toxic Goiter	Total Dose I^{131}, Mc.		
	Minimum	Maximum	Average
Diffuse	1.9	44.2	7.3
Postsurgical recurrence	1.7	22.5	5.6
Nodular	2.8	65.5	18.4

on one dose and 61% were euthyroid within three months.

The total dose of I^{131} necessary to control hyperthyroidism with each type of goiter is given in Table 5.

The incidence of hypothyroidism in radioiodine-treated patients with toxic diffuse, postsurgical recurrent, and nodular goiter are given in Table 6. Of the 309 successfully treated patients with toxic diffuse goiter, 52, or 17%, developed hypothyroidism. The incidence of hypothyroidism was greater in those controlled by a single dose of I^{131} than in the patients who required more than one dose (Table 7). Of those with postsurgical recurrence of hyperthyroidism, 22% ultimately become hypothyroid. No patient with toxic nodular goiter developed hypothyroidism. As of June, 1958, of the hypothyroidism observed, 87% had appeared within the first year after beginning radioiodine therapy (Table 8). Hypothyroidism did occur sporadically thereafter, with the longest interval so far observed between treatment and hypothyroidism being six years. From Table 8 it can be predicted that a few of the more recently treated patients are still destined to develop hypothyroidism. For this as well as other reasons, these patients should be followed indefinitely.

Less emphasis might have been placed on avoidance of post-treatment hypothyroidism and larger treatment doses of radioiodine administered (Tables 3 through 9). If at the time of the second treatment larger doses of I^{131} had been given, the number of patients requiring three or more treatments probably would have been substantially reduced. During 1946 and 1947

TABLE 6.—*Hypothyroidism and Recurrence of Thyrotoxicity in I^{131} Patients with Toxic Goiter*

Type of Goiter	Patients Becoming Hypothyroid, No.	Recurrence of Toxicity After I^{131} Treatment	
		Euthyroid After Retreatment	Hypothyroid After Retreatment
Diffuse	52	8	2
Postsurgical recurrence	16	1	0
Nodular	0	0	0
Total	68	9	2

only 13% of the toxic diffuse goiters were controlled on one dose and the incidence of hypothyroidism in this group was 11%, while for the over-all series 59% of the diffuse goiters were controlled on one dose and only 17% (Table 6) developed hypothyroidism. Thus it seems that as long as the dose is large enough to control the hyperthyroidism it is also large enough to produce hypothyroidism in some patients, and although the production of hypothyroidism can be reduced it probably cannot be prevented by giving small doses of radioiodine.

Clark and associates at The University of Chicago Clinics, who start treatment with 0.1 mc. of I^{131} per estimated gram of thyroid, have found that of 262 patients with toxic diffuse goiter, 63% were controlled by one dose and 18% became hypothyroid.[2] Chapman and Maloof, reporting on patients treated at the Massachusetts General Hospital and Harvard Medical School, have found that 75% required only

TABLE 7.—*Incidence of Hypothyroidism in Patients with Toxic Diffuse Goiter Treated with I^{131}*

Doses I^{131}, No.	Total Patients, No.	Patients Becoming Hypothyroid, No.
1	181	42 (23%)
2	75	7 (9%)
3	23	2 (9%)
4 or more	30	1 (3%)
Total	309	52 (17%)

TABLE 8.—*Hypothyroidism in Radioiodine-Treated Patients with Toxic Diffuse and Postsurgical Recurrent Goiter*

Year Treated	Time to Hypothyroidism, Mo.								
	3-4	5-6	7-8	9-12	13-24	25-48	49-72	Unknown	Total
1946-1947	1	1	1	0	0	1	1	1	6
1948-1949	4	3	0	2	0	0	0	—	9
1950-1951	3	1	2	0	0	1	0	—	7
1952-1953	9	2	0	2	1	1	?	—	15
1954-1955	14	5	2	0	3	?	?	—	24
1956-1957	7	0	0	?	?	?	?	—	7
Total	38 (56%)	12 (18%)	5 (7%)	4 (6%)	4	3	1	1	68 (100%)

one dose of I^{131} and that 8% developed myxedema when the treatment dose was approximately 0.16 mc. per gram of estimated thyroid weight.[1] From the report of Chapman and Maloof it is not clear how many of their patients developed smaller degrees of hypothyroidism. In the present series, in which the majority was treated with 0.12 mc. of I^{131} per gram of estimated thyroid weight, in patients with toxic diffuse goiter the control per single dose was 59% and the incidence of hypothyroidism was 17%. If only those patients treated in 1950 or later are considered (this includes all patients treated after adoption of the 0.12 mc. per gram dosage schedule), it is found that 154 (67%) of 229 patients with toxic diffuse goiter were controlled on one dose and the rate of production of hypothyroidism was 17%. Comparison with the data of Clark and Rule and of Chapman and Maloof indicates that by increasing the dosage the proportion of patients controlled by a single dose can be increased but that between 0.10 and 0.16 mc. per gram the increase is minimal. It also suggests that within this dosage range the proportion of patients developing hypothyroidism is about the same.

Chapman and Maloof believe that patients with untreated hyperthyroidism of short duration need doses smaller than their usual 0.16 mc. per gram of estimated thyroid weight.[1] This theory is not borne out in this study. In fact, several patients with previously untreated hyperthyroidism of short duration proved exceptionally difficult to control. For example, one patient, a woman of 46, with severe hyperthyroidism of only two months' duration and a nonnodular thyroid of about twice normal size, was treated six times with I^{131} before control was finally established; the last two doses were 0.3 and 0.4 mc. of I^{131} per gram of estimated thyroid weight, and hypothyroidism did not result. In this patient, as in several others with severe thyrotoxicosis of short duration, there was an unusually

TABLE 9.—*Number Doses of I^{131} to Produce Euthyroidism in Patients with Toxic Diffuse Goiter*

Year Treated	Doses to Euthyroidism, No.								
	1	2	3	4	5	6	7	8	Total
1945	—	—	—	1	—	—	1	—	2
1946-1947	6 (13%)	20	10	4	1	1	2	3	47
1948-1949	21 (68%)	5	—	2	1	2	—	—	31
1950-1951	26 (59%)	13	2	2	—	1	—	—	44
1952-1953	47 (76%)	9	4	2	—	—	—	—	62
1954-1955	57 (69%)	17	3	3	—	1	1	—	82
1956-1957	24 (59%)	11	4	1	—	1	—	—	41
Total	181 (59%)	75	23	15	2	6	4	3	309

TABLE 10.—*Exophthalmos in I^{131}-Treated Patients with Toxic Diffuse Goiter*

Time,* Mo.	Change in Exophthalmos After Beginning I^{131} Therapy										
	−5	−4	−3	−2	0±1	+2	+3	+4	+5	+6 to +8	Total
6-12	0	0	1	2	48	11	4	4	0	0	70
12-24	0	0	0	1	16	3	2	1	1	3†	27
24-36	0	0	0	4	16	1	1	2	0	0	24
>36	1	2	1	10	18	3	1	0	1	0	37
Total	1	2	2	17	98	18	8	7	2	3	158

* Interval between beginning I^{131} therapy and date of last data on eyes.
† Orbital decompression in one patient due to progressive exophthalmos.

rapid turnover of radioiodine by the thyroid. The initial I^{131} uptake curve showed a maximum at 3 hours, with a decrease already evident at 5 hours and very marked by 24 hours. It is now the practice to increase the dose per gram in patients who have such an uptake curve, particularly if the patient fails to show significant improvement after the initial therapy dose.

Table 6 shows that in 10 of the patients with toxic diffuse goiter, in 1 with postsurgical recurrence, and in none with toxic nodular goiter thyrotoxicosis recurred after treatment with radioiodine. All 11 patients were re-treated with radioiodine, and the final result was that 9 became euthyroid and two became hypothyroid. Thus, thyrotoxicosis recurrent after radioiodine therapy is as successfully re-treated with radioiodine as is thyrotoxicosis in patients not previously treated by this agent.

Exophthalmometric measurements were made in many patients. Whether measurements were made on a particular patient depended on who examined the patient rather than on the condition of the patient's eyes; the data can probably be accepted as representative. Any bias so introduced would be in the direction of more data on patients with severe and/or progressive exophthalmos. Measurements were made at different times by different examiners, and there is greater variability than would have occurred if all measurements had been made by a single observer. However, since in the literature data on the course of exophthalmos after I^{131} therapy are meager, the results of the present study regarding this point will be reported.

Of the 309 patients with toxic diffuse goiter, 158 had measurements made both just before and several months after therapy (Table 10). Of these, 98, or 62%, showed no change after radioiodine therapy. In 24% there was an increase of 2 mm. or more, and in 14% a decrease of 2 mm. or more was observed. Soley studied exophthalmos in patients with toxic diffuse goiter treated by subtotal thyroidectomy and in 130 patients found that 42% showed an increase of 1.5 mm. or more and 5% showed a decrease of 1.5 mm. or more.[7] Thus, as far as exophthalmos is concerned, the results of I^{131} therapy appear to be the same or slightly better than subtotal thyroidectomy.

TABLE 11.—*Eye Signs and Symptoms in I^{131}-Treated Patients with Toxic Diffuse Goiter*

Time,* Mo.	Change in Eye Signs and Symptoms After Beginning I^{131} Treatment †			
	Worse	Transiently Worse	No Change	Improved
<6	0	0	58	4
6-12	2	1	44	8
12-24	3‡	3	44	3
24-36	1	1	23	2
>36	1	4	97	6
Total	7	9	266	23

* Interval between beginning I^{131} therapy and date of last data on eyes.
† Two patients had orbital decompression before I^{131} therapy and are not included in table.
‡ Orbital decompression in 1 patient due to progressive exophthalmos.

Although only about one-half of the patients with toxic diffuse goiter had exophthalmometric measurements before and after therapy, data regarding eye signs, other than the exophthalmometric readings, and symptoms are available for all patients. Table 11 shows that of the 305 patients with toxic diffuse goiter there was no significant change in the symptoms or findings in 266. Twenty-three showed improvement, nine were transiently worse but later showed improvement at least to the pretreatment level, while in seven patients the eyes became permanently worse. Patients showing a marked or alarming change in the degree of exophthalmos, either by measurement or by other clinical finding, were placed on desiccated thyroid and a restricted salt diet and were instructed to sleep with the head of the bed elevated. One of the patients in whom the eyes became permanently worse showed an 8 mm. increase in exophthalmos, with severe persistent diplopia, photophobia, and eye pain. This patient received x-ray therapy to the space including the pituitary behind the eyes and ultimately underwent bilateral orbital decompression. As indicated in the table, two other patients had had orbital decompression before radioiodine therapy. In no eye was vision lost. Data regarding eye changes in patients with toxic nodular goiter and in those with postsurgical recurrence were too few for analysis.

In the present series there were 17 patients with toxic diffuse goiter under age 20 treated with radioiodine (Table 1). Three of these, reported elsewhere, developed nodules five years or more after the radioiodine therapy; one nodule showed invasion through its pseudocapsule.[6] Only one became hypothyroid after the initial course of therapy. Two had recurrence of hyperthyroidism and were re-treated with radioiodine. One of the latter ultimately became hypothyroid.

As noted earlier, death occurred in three patients with uncontrolled thyrotoxicity, but in no case was there evidence that exacerbation of thyrotoxicity by the radioiodine was a factor in the death. In one patient, chronic leukemia was diagnosed three years after radioiodine therapy. A review of the earlier record of this patient disclosed that an elevated white blood cell count and a significantly enlarged spleen were present previous to the radioiodine therapy, and this patient probably had undiagnosed leukemia previous to radioiodine therapy.

Summary

Prior to June, 1957, four hundred thirty-one patients with thyrotoxicosis were treated with I^{131} at the University of California School of Medicine in San Francisco. Of these, 29 had toxic nodular goiter; 78 had postsurgical recurrent toxic goiter, and 324 had toxic diffuse goiter. In 95% toxicity was controlled with radioiodine; therapy in the other 5% was incomplete. Thyrotoxicity was controlled in 59% by one treatment, and 61% became euthyroid within three months.

As defined here, hypothyroidism developed in 17% and recurrence in 3% of the toxic diffuse goiters. That hypothyroidism or recurrence may follow I^{131} therapy is certain; however, the incidence depends on the definition of terms. When hypothyroidism occurred, it was usually seen within a few months; however, in one case it did not appear until the sixth year after therapy.

Exophthalmos may improve, appear, or progress after radioiodine therapy. Although comparison is difficult, it would appear that in this respect the results are about the same or slightly better than after surgical subtotal thyroidectomy. Orbital decompression became necessary in one patient, but in no case was vision lost.

There was one unexplained death three weeks after treatment with I^{131}. Three patients under 20 years of age developed thyroid nodules five or more years after therapy.

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Tissue Specificity of Serum Components

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Introduction

Serum proteins incorporate amino acids very rapidly, and it seems justifiable to conclude that this process takes place within cells somewhere in the body, whether by synthesis *de novo* or by some sort of exchange in the cell between serum proteins and amino acids. Implicit in the latter is the assumption that circulating serum proteins continuously return to cells of origin. In recent years it has been found that serum proteins do indeed pass from the blood stream into cells of many of the body tissues.[1,4,7,9,10,16,17,21,26,28,31,32,34,39] Also, recent evidence indicates that serum proteins are utilized metabolically by cells. Both albumins and globulins appear to be involved in these cellular relationships.[39-41]

On the other hand, proteins of many kinds are elaborated by body tissues and appear in various extracellular fluids. The serum proteins, composed of a number of different molecular species, represent at least a considerable fraction of these. The glands of external and internal secretion provide many extracellular proteins, such as enzymes, insulin, adrenocorticotropic hormones, and others. In addition proteins appear in the blood either in increased amounts or newly formed under many pathological conditions that suggest their derivation from various tissues. Thus a number of enzymes and other proteins are known to circulate as globulins in the serum of normal and ill persons, such as phosphatase, transaminase, pepsin, cholinesterase, and amylase, globulins thought responsible at least in part for various flocculation phenomena, such as the cephalin flocculation test, unusual β-globulins, C-reactive protein, glycoprotein, antibodies, and numerous others. These must be derived of course from one or more tissues. The association of serum acid phosphatase concentrations with prostatic disease, serum alkaline phosphatase with bone and liver disease, and serum transaminase with liver and heart diseases is suggestive of a plurality of tissue origins for these proteins.

It would appear that cell membranes are somehow and at times permeable to certain of their own intracellular proteins. They are also permeable to the circulating serum proteins, with some as yet unknown degree of selectivity.

A theory of cell response to damage was evolved in this laboratory[42] and together with the above facts has led us to the derived hypothesis that serum globulins have a cellular origin from a large variety or perhaps all of the tissues of the body. It is also predicted that they consist in part (or entirely, depending on a new, derived theory of antibody formation[42]) of normal cell proteins that regularly escape from the cells of various tissues and circulate in

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body fluids. It is expected that these extracellular proteins then reenter their respective cells of origin, wherein they take part in the same protein metabolism in which they were involved before leaving the cell.

Although the origin of the various parts of the serum globulins has remained obscure, it is obvious that they all must arise from one or more tissues in the body. Lymph node, spleen, bone marrow, liver, and other tissues have been suspected of giving rise to some serum globulins at times. Miller, Bly, and Bale have shown by perfusion experiments that rat liver can make albumin and α- and β-globulins, while peripheral tissues can elaborate small amounts of γ-globulin.[27] Study of cases of hypergammaglobulinemia has indicated a possible role for the plasma cell [2,8]; so also have studies in animals of response to injected antigens.[13] Antibodies have the physical-chemical properties found in serum globulins, in fact most antibodies are indistinguishable from γ-globulins except by antibody function.[6] Numerous studies have implicated lymph nodes and lymphocytes, plasma cells, spleen, and possibly other tissues as sources of antibody.[18]

Specific tissue antigenicity now seems to be established.[3,12,14,15,19,22,24,25,29,30,33,36-38] Therefore, if some or all of the hypothetically released and circulating tissue proteins were to have the structural specificity of their tissues of origin, it might be feasible to estimate their presence in serum by antiserum made specific for various tissues. This has been tried, and each antiserum so made has demonstrated the presence of an independently varying component of human serum.

Experimental Approach

A 0.2 ml. amount of successive twofold dilutions of human serum was mixed with 0.2 ml. of each of several rabbit antisera at various twofold dilutions, each antiserum having been made by intravenous administration of organ extracts of human tissue. After 48 hours the greatest dilution of the human serum showing macroscopic precipitin was recorded and plotted on a graph, with time units on the abscissa. Various factors in production of reliable results were explored and are set forth in this section as our critical evaluation of the approach.

Antisera.—Specificity of the antisera, as taken from the rabbit, differed greatly with the organ used.[5] Antihuman thyroid serum was much more specific than most of the others; on the other hand, antihuman lymph node serum was probably the most widely cross reactive serum obtained, its cross reactivity being shown in Table 1 (Column 2, "crude"). In Tables 2, 3, 4, 7, and 11 the figures represent a visual estimation of the amount of precipitin in each instance and are to be compared roughly with each other and with the complete absence of precipitin where indicated. In Table 1 (Column 1 "crude"), in Table 3 ("crude antiliver" and "crude antikidney" horizontal lines), and in Table 4 (the horizontal blocks marked "crude") one may see evidence for cross reactivity of crude antiserum with various organ extracts. Liver and kidney antisera were usually especially cross reactive with kidney and liver, respectively, as indicated by the values in italics in Table 3. But at a dilution of 40-fold, antiserum for guinea pig liver was unreactive with kidney extract (see second horizontal line of values, Table 4).

Antithyroid serum sometimes could be used without preabsorption of cross reactivity, as will be reported later. For the other antisera, cross reactivity was reduced by addition of certain tissue suspensions before they were mixed with unknown human sera. Various antisera, untreated by tissue addition, were tested by agar diffusion [35] and gave lines of interaction with several organ extracts in each case, except for antihuman thyroid sera, for which only thyroid extract produced lines.

"Absorbed" Antisera.—As shown by others and confirmed here, addition of certain tissue suspensions to an antiserum could be used to remove cross reactivity and make an antiserum specific for an individual tissue over an appropriate range of dilutions of tissue extract and of antiserum. In Table 1 the effect of using these

TABLE 1.—*Reactivity of Antihuman Sera* *

Test Antigen (Human Organ Extract) Diluted	(1) Antiserum to Kidney		(2) Antiserum to Lymph Node		(3) Absorbed Antiserum to		(4) Absorbed Antiserum to Liver		(5) Absorbed Antiserum to Liver		(6) Absorbed Antiserum to Kidney		(7) Absorbed Antiserum to Kidney	
	Crude	Absorbed	Crude	Absorbed	Liver	Kidney †	Fold Dilution of Antigen							
	20	20	20	20	50	50	50	100	50	100	50	100	50	100
Liver	6 †	2	8	0	4	0	3	2	6	2	0	0	0	0
Kidney	8	5	8	0	0	4	1	0	0	0	2	5	2	6
Pericardium	6	0	8	2	0	0	0	1	—	—	0	0	—	—
Lymph node	6	0	9	9	0	0	0	0	2	0	0	0	2	0
Heart	6	0	8	0	0	0	0	0	1	0	0	0	2	0
Muscle	4	0	8	0	0	0	0	0	0	0	0	0	0	0
Brain	2	2	8	0	0	0	0	0	1	0	0	0	0	0
Skin	2	0	8	0	0	0	0	0	0	0	0	0	0	0
Spleen	6	0	8	0	1	0	0	0	3	0	0	0	0	0
Red cells	4	2	6	0	0	0	0	1	0	0	0	0	0	0
Intima, aorta							0	1	1	0	0	0	0	0

* Columns 1 and 2, absorbed with human pericardium only; antiserum tested at 2-fold dilution; columns 3-7, antiserum tested at 8-fold dilution.
† Numbers indicate amounts of precipitin observed, see "Experimental."

TABLE 2.—*Specificity of Absorbed Antihuman Sera at Various Dilutions*

	Fold Dilution of Antisera	Antihuman Serum, Partly Absorbed																			
		Human Liver Extract				Human Kidney Extract				Human Heart Extract				Human Lymph Node Extract				Human Spleen Extract			
		Fold Dilution of Antigen																			
		20	50	100	200	20	50	100	200	20	50	100	200	20	50	100	200	20	50	100	200
Antiliver	4	3 *	2	0	2	3	3	3	2	3	3	4	5	3	4	3	3	4	3	5	4
	8	3	2	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Antikidney	4	0	0	0	0	7	5	4	0	1	0	0	0	0	0	0	0	3	3	2	0
	8	2	0	0	0	5	6	7	3	0	0	1	0	2	0	0	0	5	3	1	0

* Numbers indicate amount of precipitin.

TABLE 3.—*Effect of Absorption of Antihuman Sera on Cross Reactivity*

Antihuman Serum	Fold Dilution of Antisera	Human Organ Extract: Liver 100	Kidney 100	Spleen 100	Heart 100	Muscle 100	Liver Fold Dilution of Antigen 20	Liver 50	Kidney 20	Kidney 50	Spleen 20	Spleen 50	Heart 20	Heart 50	Muscle 20	Muscle 50
Crude antiliver	8	8	7	4	3	0										
	16	7	6	4	0	0										
	32	5	3	0	0	0										
Absorbed antiliver	4						4	4	2	0	0	0	0	0	0	0
	8						3	2	0	0	0	0	0	0	0	0
	16						2	1	0	0	0	0	0	0	0	0
Crude antikidney	8	8	7	4	4	0										
	16	7	7	2	3	0										
	32	5	4	3	0	0										
Absorbed antikidney	4						3	0	5	3	0	0	0	0	0	0
	8						2	0	3	2	0	0	0	0	0	0
	16						0	0	2	0	0	0	0	0	0	0

TABLE 4.—*Effect of Absorption of Antiserum to Guinea Pig Liver*

Fold Dilution of Antiliver Serum	Guinea Pig Liver Extract: Fold Dilution of Antigen 10	40	160	640	2,560	Guinea Pig Kidney Extract: 10	40	160	640	2,560
Crude										
10	3*	4	3	2	0	4	4	4	3	0
40	2	2	4	3	0	0	0	0	0	0
160	0	0	0	0	0	0	0	0	0	0
320	0	0	0	0	0	0	0	0	0	0
Absorbed †										
10		4	4	3	0		0	0	0	0
40		0	0	0	0		0	0	0	0
160		0	0	0	0		0	0	0	0
320							0	0	0	0

* Numbers indicate amount of precipitin.
† Absorbed with muscle, heart, and kidney.

TABLE 5.—*Repetition of Precipitin Test by Two Observers* *

Antiserum Antigen Used †	Observer No. 1	No. 2
Liver-liver	128	256
Kidney-kidney	256	256
Lymph-lymph node	128	256
Heart-heart	512	256

* Values expressed as maximum dilution of patient's serum.
† These antisera had been made organ-specific by absorption.

TABLE 6.—*Results from Different Preparations of Antisera* *

	Antiserum, Batch No. † 11	13	14	15
End-point	32	32	32	128

* Values expressed as maximum dilution of patient's serum.
† Antisera were previously absorbed and made organ-specific. No. 15, however, was found later not to have stayed specific, and reabsorption was needed.

TABLE 7.—*Effect of Storage of Partly Absorbed Antisera to Guinea Pig Tissues at —20 C*

Partly Absorbed Antiserum	Fold Dilution of Antiserum	Guinea Pig Organ Antigen: Kidney		Liver		Spleen		Muscle		Heart	
		Fold Dilution of Antigen: 50	100	50	100	50	100	50	100	50	100
Antiliver, original	4	4 *		7		2		0		0	
	8	3		4		1		0		0	
	16	2		3		0		0		0	
Antiliver, after 45 days of storage	4	0	0	1	0	0	0	0	0	0	0
	8	0	0	0	0	0	0	0	0	0	0
	16	0	0	0	0	0	0	0	0	0	0
Antikidney, original	4	5		3		3		0		0	
	8	4		2		2		0		0	
	16	2		0		0		0		0	
Antikidney, after 45 days of storage	4	3	2	1	0	2	2	0	0	0	0
	8	3	2	0	0	0	0	0	0	0	0
	16	3	0	0	0	0	0	0	0	0	0

* Numbers indicate amount of precipitin.

TABLE 8.—*Species Interactions: Crude Antiserum to Guinea Pig Pancreas*

Fold Dilution of Antiserum	Precipitin Test *: Human Pancreas Antigen, Fold Dilution of Antigen: 20	40	80	160	Guinea Pig Pancreas Antigen, Fold Dilution of Antigen: 20	40	80	160
8	3	1	0	0	6	6	6	6
16	2	1	0	0	2	1	2	3
32	0	0	0	0	1	0	0	0
64	0	0	0	0	0	0	0	0
128	0	0	0	0	0	0	0	0

* Complement-fixation test showed complete hemolysis for all dilutions of human pancreas titrated against dilutions of anti-guinea-pig serum; while the latter, when titrated against guinea pig pancreas, gave incomplete hemolysis as far out as an antiserum dilution of 128 and an antigen dilution of 2,500-fold.

† Numbers indicate amounts of precipitin.

TABLE 9.—*Effect of Incubation and Standing on Human Liver-Antiliver System*

Incubate: Hr.	Temp.	Stand: Hr.	Temp.	Fold Dilution of Antiserum: 16	32	64	128	256
1	37 C	0		5 *	5	4	4	3
1	37 C	24	4 C	6	6	5	5	4
1	37 C	48	4 C	6	6	2	0 †	4
3	37 C	48	4 C	6	4	5	0 †	4

* Numbers indicate amounts of precipitin.

† These 2 deviations are unexpected, caused by some hidden error.

TABLE 10.—*Effect of Varying the Force and Time of Centrifugation*

Force, Tip of Tube, g *	Min.	Fold Dilution of Antihuman Liver Serum: 4	8	16	32	64	128
1,292	5	8 †	8	7	3	2	1
1,292	15	8	8	7	2	1	1
1,292	30	8	8	7	2	3	2
1,292	60	8	7	7	0	3	2

* Gravitational force units.

† Numbers indicate amounts of precipitin.

TABLE 11.—*Precipitin Formation—Antihuman Thyroid Serum, Crude*

Antiserum to Human Thyroid, Fold Dilutions	Human Antigen *																									
	Thyroid					Kidney					Spleen					Pericardium					Blood Vessel					Liver Dil. No. 1	Heart Dil. No. 1	Lymph Node Dil. No. 1	Muscle Dil. No. 1
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5				
Concentrated		9	6	0	0		3	0	0	0		5	0	0	0		6	0	0	0		0	0	0	0				
8	8†					6					9					6					7					0	5	4	7
16	4					2					8					4					5					0	5	3	3
32	2					0					4					3					3					0	4	3	0
64	1					0					3					0					0					0	3	3	0
128	0					0					0					0					0					0	0	0	0

* Fold dilution of antigen for No. 1, 2, 3, 4, and 5, respectively, are 50, 2,500, 25×10^3, 25×10^4, 25×10^5.

† Numbers indicate amounts of precipitin.

"absorption" methods is compared in Columns 1 and 2 with that of using the untreated, "crude" antiserum. The other five columns show the specificity obtained with "absorbed" antisera to liver and kidney.

In Table 2 great improvement is seen in the specificity of two antisera after addition of certain tissue suspensions for reduction of cross reactivity, although it is apparent that the antikidney serum needs still further treatment for its cross reactivity to spleen. In Table 3 other antiliver and antikidney sera are compared before and after absorption (note italics), the improvement after absorption being present at very high concentrations of antigen.

In Table 4 the marked increase in specificity after absorption of another antiliver serum is shown. The most difficult cross reactivities to overcome were found to be those between liver and kidney extracts and their respective antisera.

Addition of excessive amounts of tissue suspension, beyond that necessary to eliminate cross reactivity for an appropriate range of dilution of antiserum, caused at times some weakening of the specific reactivity of the antiserum. Addition of one tissue was usually adequate to reduce most of the cross reactivity, connective tissue or lymph node being the most effective. However rabbit antisera of low antibody response were not successfully "absorbed."

Reproducibility.—Repetition of the entire precipitin test at the same time on the same human serum by two different persons, independently, gave similar results for reading the point of maximum dilution, Table 5. Error is of the order of one dilution (twofold) as a maximum. For a single person repetition gave the same result with a shift by one dilution in about 10% of readings.

Repetition with different batches of antisera gave a good degree of correspondence, as seen in the results of several different antisera, Table 6. However, in spite of this, comparison of human or animal results was not made in this report unless the same

TABLE 12.—*Complement Fixation**

Antiserum to Human Thyroid, Fold Dilution	Human Antigen, Fold Dilution †																											
	10			40			160			640			2,560			10,240			40,960			163,840			Control		
	T	K	L	T	K	L	T	K	L	T	K	L	T	K	L	T	K	L	T	K	L	T	K	L	T	K	L
10	0	0	2	0	1	3	2	4	4	1	4	4	0	4	4	0	4	4	0	4	4	1	4	4	4	4	4
40	0	1	3	0	4	4	3	4	4	4	4	4	0	4	4	0	4	4	0	4	4	1	4	4	4	4	4
160	0	2	4	1	4	4	4	4	4	4	4	4	3	4	4	0	4	4	1	4	4	2	4	4	4	4	4
640	2	4	4	4	4	4	4	4	4	4	4	4	3	4	4	0	4	4	3	4	4	4	4	4	4	4	4
2,560	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
10,240	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Control	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4

* Values expressed as approximate degrees of hemolysis: full hemolysis, 4; no hemolysis, 0; partial hemolysis, grades 1, 2, and 3.
† T indicates thyroid antigen; L, liver antigen; K, kidney antigen.

antisera were used throughout the period of comparison.

Variables.—It would be expected that *crude* antisera would remain stable at temperatures of −20 C, and over a three-month period this was found to be true for antisera to both human and guinea pig organs. Absorbed, tissue-specific antisera were not always as stable; it was found well to check antisera specificity after a month, and after three to four months this may be considerably altered (Table 7; note values in italics).

Dilution of antiserum tended to increase its specificity, as shown in Tables 2, 3, 4, 7, and 8. This was true for both crude and absorbed sera and fits the known general effect of dilution of antigen or of antibody concentration.

From Tables 9 and 10 it will be seen that within the limits measured no effect of change in incubation time, standing time at 4 C, or centrifugal force could be found.

Complement Fixation.—Complement-fixation measurements with crude unabsorbed antisera and patient's sera yielded results highly confirmatory of the precipitin ones, Tables 11 and 12.

As expected, the precipitin test was less sensitive than the former. Thus in Tables 11 and 12, precipitins permitted dilution of crude antithyroid serum 64-fold and thyroid antigen 25,000-fold, while complement fixation permitted dilution of antiserum 640-fold and of thyroid antigen 164,000-fold. The correlation shown here when crude antisera are used suggests a useful degree of specificity both for these crude sera and for the complement-fixation test.

Results

In Figure 1 are plotted the serum dilution limits of four normal persons as measured by precipitin formation with four different absorbed antisera. It is apparent that each antiserum gives very different dilution limits for each person, and no constant pattern is discernible. One person, FB, showed much reduced limits for all antisera and the

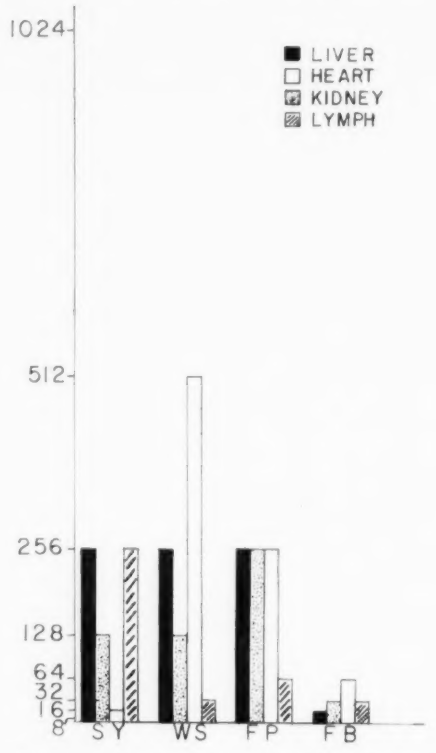

Fig. 1.—Variation of four precipitating components in serum of four normal persons. Ordinate values represent serum dilution in all figures.

electrophoretic pattern showed a reduction in γ-globulin to about 0.7 gm. %. Figure 2A shows that the low values found for FB in Figure 1 remained very low for three weeks. On the other hand, two other normal persons with normal serum electrophoresis (paper) showed wide fluctuations in dilution limits (Fig. 2B and C).

In each of the latter figures it is very clear that each dilution limit in the same serum varies with time entirely independently of the others. Thus each antiserum must react with completely separate components in human serum. This is especially well illustrated in the case of liver and kidney, for each of which crude antiserum in vitro tends to cross react with the other organ very strongly; in fact special absorption efforts are required to remove this

Fig. 2A.—Variation of four precipitating components in serum at different times in one normal person.

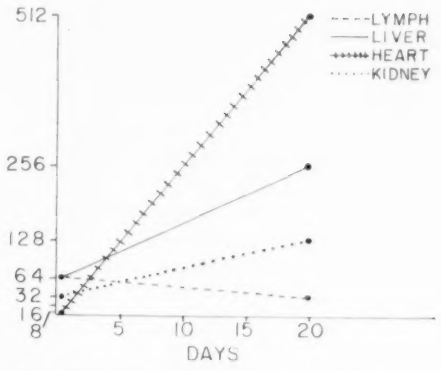

Fig. 2B.—Variation of four precipitating components in serum at different times in one normal person.

effect. Yet, in Figures 2C, 3, and 4, one sees the curves of dilution limits for liver crossing those of the kidney at right angles.

Figures 3 and 4 show the results of measurements made on two known cases of coronary occlusion. It is apparent that

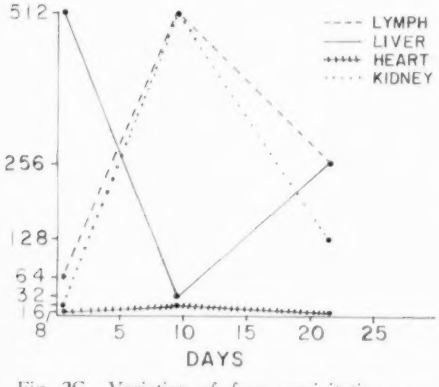

Fig. 2C.—Variation of four precipitating components in serum at different times in one normal person.

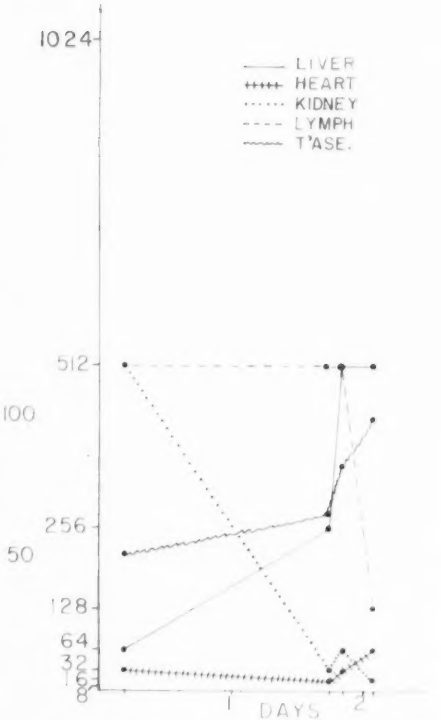

Fig. 3.—Variation of four precipitating components in serum in case of myocardial infarction. Patient was 53 years old, died in two days; confirmed by postmortem examination; congestive heart failure; transaminase activity was 100 units at the time of death. First day (abscissa) is first day of illness.

fluctuations in dilution limits occur both in normal persons and in these two cases. These variations are of course not surprising in view of the great possibilities that could exist for shifts between serological and cellular phases of circulating proteins. Present conceptions of continual circulation of all serum proteins through extravascular spaces and cells (Introduction) provide a basis for serum to reflect changes in tissues and cells very quickly and continually.

For each kind of human serum components there are several instances in which the dilution limit was reduced from higher values to such a degree as to indicate only a little of that kind of antigen in the circu-

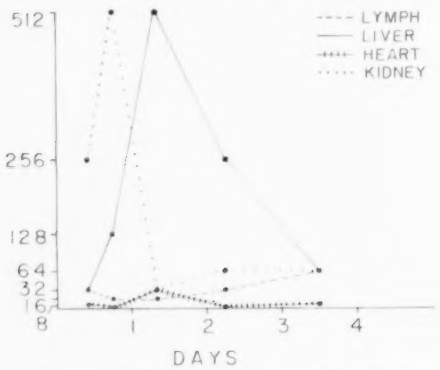

Fig. 4.—Variation of four precipitating components in serum of a case of myocardial infarction. Patient was 48 years old; hypertension, ECG findings typical, discharged improved. First day (abscissa) is fifth of illness, transaminase not increased.

lating blood, e. g., liver in Figure 2C, kidney in Figure 3, kidney and liver in Figure 4. In none of these cases were there major changes in serum protein concentration, total albumin and globulin concentrations, and, where tested, in electrophoretic patterns. It is clear from this and the fact of variability of each component independently that the antisera are not directed toward serum globulins (or albumins) as a group. This is possibly explained by the presence of only small amounts of the latter substances in the tissue antigens given to rabbits and was demonstrated previously through retention of tissue-specific antibodies in spite of

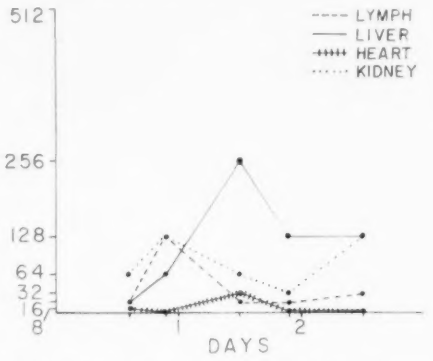

Fig. 5.—Variation of four precipitating components in serum of a case of myocardial damage. Patient was 44 years old; severe precordial pain, prostration, T and S-T changes, transaminase not increased, improved at discharge. First day (abscissa) is third of illness.

neutralizing the cross reactivity of the antisera with tissue antigens containing serum proteins. It is not possible to explain the results or even the preparation of specific antisera by presence of antibodies to serum globulins as a whole.

Altogether 105 pathological sera from 37 patients have been analyzed for evidence of circulating protein constituents from certain tissues. The results mentioned (Figs. 3 to 12, inclusive) were obtained with antisera to human liver, kidney, lymph node, and heart. Specific antisera were made also to

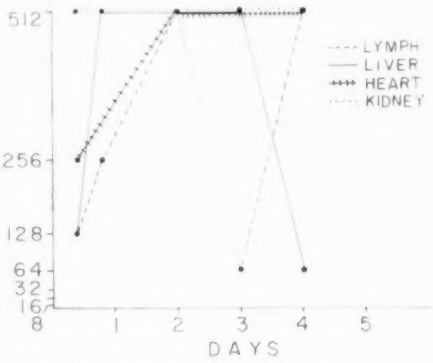

Fig. 6.—Variation of four precipitating components in serum of a case of acute myocardial posterior infarction. Patient was 49 years old; typical ECG findings, discharged improved, transaminase was 120 units on second day of illness. First day (abscissa) is also first day of illness.

Fig. 7.—Variation of four precipitating components in serum of case of infectious hepatitis. Patient was 35 years old; jaundice, abnormal liver-function tests; first day (abscissa) is eighth day of illness, patient improved after this day; complete recovery.

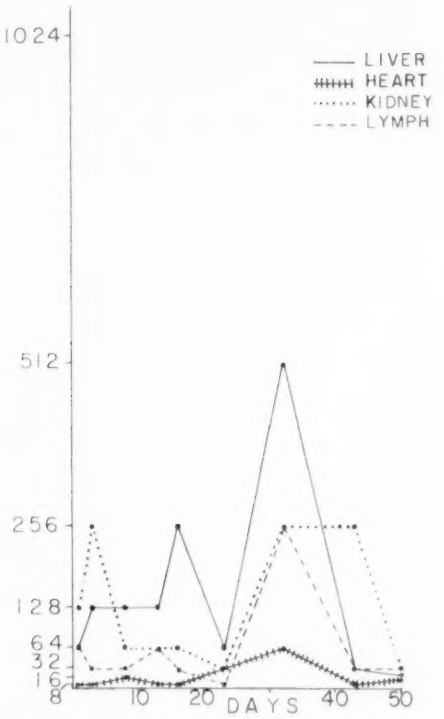

Fig. 8.—Variation of four precipitating components in serum of a case of infectious hepatitis. Patient was 33 years old; jaundice, abnormal liver-function tests; first day (abscissa) is fifth day of illness; complete recovery.

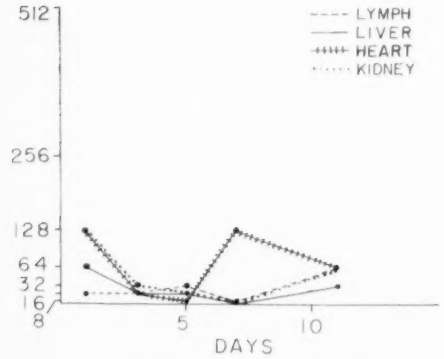

Fig. 9.—Variation of four precipitating components in serum of a case of hepatitis, suspected Weil's disease. Patient was 45 years old; chills, fever, jaundice, leptospiral agglutination titer 1:3,200; discharged recovered. First day (abscissa) is 20th day of illness.

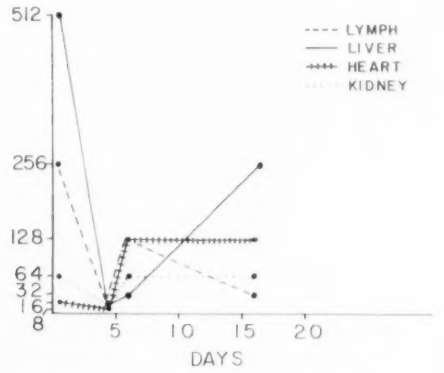

Fig. 10. Variation of four precipitating components in serum of a case of adenocarcinoma of head of pancreas. Patient was 55 years old; operation on third day; discharged improved.

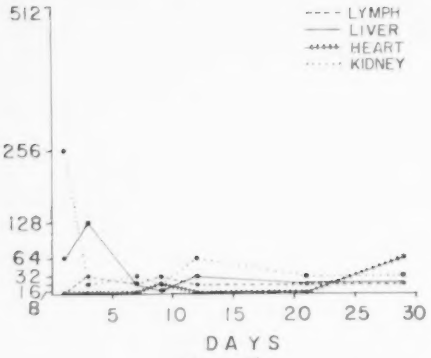

Figure 11

Fig. 11.—Variation of four precipitating components in serum of a case of renal disease. Patient was 46 years old; chronic glomerulonephritis, inactive nephrotic stage, not improved. First day (abscissa) is approximately 14th day after acute exacerbation.

Fig. 12.—Variation of four precipitating components in serum of a case of renal disease. Patient was 28 years old; chronic glomerulonephritis in acute nephrotic stage, discharged improved. First day (abscissa) is 14th after admission. Onset of acute exacerbation about four days before admission.

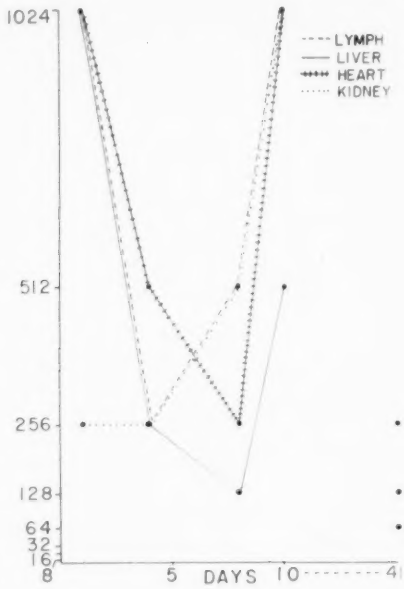

Figure 12

human brain, spleen, muscle, mucosa of colon, skin, intima of aorta, and red cells; these have been tested only in limited ways but show very similar relationships, in general.

It may be seen from these results, too, that each of the various specific rabbit sera reacts with apparently different components of human serum to an independently varying degree. The great variability in these cases does not permit any conclusions about tissue activity in a given disease; much further study must be done. On the other hand, variability was predictable in view of the many expected but unknown alterations in organ activity in disease together with the probable complexity of the interactions between antisera and the proteins in question.

The maximum dilution limit found for 0.2 ml. human serum was 4,000-fold by use of concentrated antiserum for lymph node constituents in a case of lymphosarcoma. It was unusual, however, to find evidence of serum components in dilutions of human serum greater than 512-fold for 0.2 ml. of serum. In a case of exfoliative dermatitis (results not graphed), kidney, lymph node, and liver constituents of serum all showed greater dilution limits than 512 over a 27-day period. The eight cases of cardiac infarct all showed a rise in liver components but none in heart components except for one (e. g., Figs. 3, 4, 5, and 6).

By the immunoelectrophoretic method[35] we have found so far crescents of precipitin opposite β- and γ-globulin fractions of human sera with use of various rabbit antisera.

Almost without exception, for most organ antigens each rabbit developed useful antisera, each of approximately the same strength, as determined by a dilution limit of about 64-fold for 0.2 ml. of the antiserum. A poor response was always found with certain of the organs however, such as brain and skin and, to less extent, heart. Also, more than one-half of the rabbits receiving human brain died during the third week of injection, always suddenly, about two to five minutes after an intravenous injection of human brain tissue. Routine

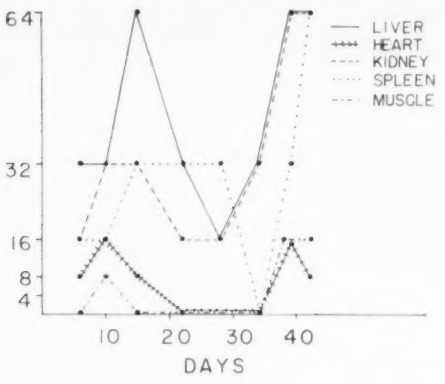

Fig. 13.—Rabbit antiserum: Antibody response to injected guinea pig liver, showing cross reactivity of various degrees to organ antigens. Days (abscissa) indicate time after last injection of antigen; booster dose of antigen injected on 34th day.

sections of organs of immunized rabbits were obtained, and the results may be reported at a later date.

Antiserum reactivity was followed for some time in a number of rabbits (Fig. 13). Booster injections of antigen were explored somewhat and were occasionally found helpful, as shown. Zone electrophoresis of several rabbit antisera showed definite increase in γ-globulin after the course of injections. After absorption with tissue several antisera were again subjected to zone electrophoresis and found to have lost up to 50% (approximately) of the original concentration of γ-globulin.

Experimental Methods

A. Preparation of Organ Antigens.—Human tissues (kidney, muscle, skin, thyroid) were obtained freshly in the operating room when possible; human heart, brain, liver, spleen, lymph node, aorta, and connective tissue were obtained about 6-12 hours post mortem, avoiding extremes of patient age and of disease. Guinea pig tissues were taken from freshly killed pigs. All tissues were kept sterile throughout the rest of the procedure. After gross blood was quickly washed off with saline and gross amounts of vascular, connective, and fat tissue were dissected away, the tissues were stored at —20 C for no longer than six months, when they were discarded. During this period tests showed no bacterial growth on blood agar or any odor or other apparent change.

For preparation of antigen, part of the tissue was thawed but never allowed to warm above 4 C or 5 C during any part of the ensuing procedure. After being homogenized in a Waring Blendor in 10- to 30-second bursts at 0 to 5 C, the tissue was pressed gently through a stainless steel sieve (16 mesh per inch, pores 1.0 mm.^{2}) to remove more blood vessels and connective tissues. It was then rehomogenized briefly in 4 vol. of 0.15 N aqueous sodium chloride and passed through three layers of sterile gauze, after which it could be injected through a No. 25 needle subcutaneously.

For injection into rabbits the material was used at first as a suspension in saline, the concentration of the original suspension or its centrifuged supernatant being called 100% (although actually diluted with 4 vol. of saline, as above). Lately we have tended to use the clear supernatant of this suspension (after adequate centrifuging). The original suspension contained 2 to 4 mg. of nitrogen (Kjeldahl) per milliliter for each organ except skin, brain, and intima of aorta, each of these having about 1 mg. of nitrogen per milliliter. Zone electrophoresis showed no "albumin" spot for any of the tissues; most of the proteins had a migration rate about equal to that of serum γ- and β-globulins.

B. Immunization of Rabbits.—Two to four rabbits, white, male, Rockland, 2.5 to 4 kg. in weight, were given intravenous injections with a given organ preparation, beginning with 0.2 mg. of nitrogen per day and gradually increasing this over a three-week period through daily doses five times a week to 2.0 mg. of nitrogen. In 15 injections a total of 12-24 mg. of nitrogen was given. If antisera did not show adequate level of antibodies on removal of blood from the heart on the 7th and 10th days after the course of injections, antigen administration was carried on for another week.

C. Absorption of Antisera.—Cross reactivity was removed for certain ranges of dilution of antigen and antiserum by judicial, step-wise addition of small increments of whole-organ suspensions (or supernatant of extract) to the antiserum, the latter usually diluted fourfold for the purpose. Before absorbing antigenic preparations were added, it was found necessary to test the crude antiserum at various dilutions against a large variety of organ antigens. Sometimes the addition of absorbing tissue was followed by incubation at 37.5 C for one to two hours before it was allowed to stand in the refrigerator, but usually the higher temperature was avoided to prevent appreciable proteolytic activity on the part of the added tissue; the mixture was then kept at 4 C for 48 hours. Clear supernatant was removed after centrifuging in the cold (4,700 g at tip of tube), tested at scattered dilutions for results, and then treated further if necessary. To avoid excess of organ extract it is

important to add at time of each increment only about one-fifth of the total amount of extract needed, as determined by pretesting, trial and error, and previous experience.

D. Modified Precipitin Test, Complement Fixation.—The precipitin test was used to estimate the possible limits of unknown serum or of antigen dilution giving visible precipitin. It was also used to approximate the order of magnitude of the antigen-antibody precipitate for certain practical purposes. It was performed in standard fashion,[20] with 0.2 ml. of diluted antiserum and 0.2 ml. of diluted clear organ extract mixed in the tip of a 12 ml. glass pointed centrifuge tube. The organ extract usually had to be recentrifuged several times before use in order to obtain no precipitate in the control test with 0.15 N sodium chloride solution. Fiftyfold dilution of "100%" organ (see third paragraph under Preparation of Organ Antigens, above) extract was labeled 50-fold. Except for incubation after mixing, all materials were continuously surrounded by ice water and between use were stored daily at −20 C.

Tubes were covered with aluminum foil throughout the test to avoid dust and minimize evaporation. Complete tests comprised a series of twofold dilutions of antigens and for each of these a series of twofold dilutions of antiserum. The test solutions after incubation at 37.5 C for one-half hour were held at 4 C for 48 hours, then centrifuged at 4 C for 15 minutes at about 1,300 g (at tip of tube), and with good indirect lighting and a dark background the result was read approximately as estimated amount of precipitate expressed as exponent of base 2, the smallest visible trace to the unaided eye being assigned the exponent 1. Dilution limit was recorded as the dilution of the last tube showing a visible trace of precipitin to the eye. The character of the precipitin was always confirmed by use of a magnifying glass (×14).

To insure as great specificity as possible the following steps were taken: 1. Antisera were employed at concentrations even less than those found to give a complete or very high degree of organ specificity. 2. Antigen was estimated by limit of dilution, so that results were based on effects at antigen concentrations far removed from those showing even traces of cross reactivity in control tests. 3. Weak antisera were not used. 4. Denaturation of antigen was avoided as far as possible by avoidance of potentially harmful conditions in preparation (see Experimental Methods).

The following control precipitin tests were made repeatedly: normal rabbit serum diluted eightfold and mixed with normal and abnormal human serum at various dilutions, rabbit antiserum diluted with saline, human sera diluted with saline, frequently repeated checks of specificity of stored rabbit antisera, mixing of human tissue extracts in appropriately diluted normal rabbit serum, and testing of this for precipitins with serum of patients. All of these tests gave negative results in every case.

Complement-fixation tests were run in standard fashion.[20]

Conclusions

The results show that the antisera prepared from another species, with relative specificity for mixed components of a single human organ in saline extract, will fractionate parts of the serum proteins of individual persons by production of precipitins. Direct proof that it is serum *proteins* that react with the antisera is lacking, but it is very doubtful that proteins are not taking part in the reaction in view of the predominance of proteins in the sera, the fine distinctions of specificity between tissues, evidence from immunoelectrophoresis, and the prominence of protein in the antigens used. The results are reproducible; also each person at various times has a different pattern of precipitin fractions, measured by limit of serum dilution. These facts indicate that serum proteins are certainly not homogeneous but can be divided into many independent fractions by these antitissue sera.

These components of normal and pathological human serum thus show tissue specificity. One wonders whether they may be derived from the tissues corresponding to the antisera used. That each antiserum may somehow cross react with other serum fractions not derived from the corresponding tissue remains to be tested further and is under investigation in this laboratory.

Variation in dilution limits of serum for each antiserum was notable between individual cases and in the same subject over a time period. Theoretical derivation predicts this[42] on the basis of a changing activity of tissues in response to all kinds of conditions. It is not possible to calculate accurately what fraction of the serum proteins are represented by the total components discerned here, but a crude approximation may be made as follows: Assuming that the precipitins are composed of γ-globulin as their antigen component, in 0.2 ml. of

serum there is normally about 0.3 mg. of nitrogen from γ-globulin, and, if this is divided equally among 10 possibly contributing tissues, about 0.03 mg. of γ-globulin nitrogen from each of the 10 tissues might be present in 0.2 ml. of serum. If the limit of nitrogen as protein antigen required for a positive precipitin reaction is 0.1μg., then a dilution limit of 100-fold for a tested serum indicates that 10 of the expected 30μg. can be accounted for. If more than 10 tissues are represented or if dilution end-points exceed 100-fold, as they often did, then a large fraction of the expected constituents are so measured.

Or, again a found dilution end-point of 500-fold for 0.2 ml. of serum theoretically represents 5,000-fold for 2 ml. of serum. If there were only 10 tissues represented the concentration of each might be roughly one-tenth of the concentration of serum globulin as a whole; i. e., if *each* tissue antigen were present in 10 times its expected normal concentration our present dilution end-point would be 50,000-fold for 2 ml. of serum. This corresponds favorably with the dilution limits of serum in presence of antiserum to whole serum, i. e., 200,000- to 500,000-fold. Further, the antisera used in these experiments have been much "weakened" by absorption with tissues.

These facts help to confirm the concept developed from work on tissue damage, that proteins derived from many tissues may circulate as serum proteins, probably as globulins. The results suggest that tissue identity may not be restricted to a small part of the serum globulins and *may* even apply to all, although no certain statements about this can be made at this time. Further steps are being taken to obtain more quantitative data. The results also provide further evidence that tissue specificity does exist in the mammal.

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The Azosulfamide (Neoprontosil) Test in Clinical Evaluation of Liver Function

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In 1951, Siede and Strohm [1] suggested a liver-function test with a sulfonamide preparation, the red dye azosulfamide (Prontosil Soluble, Bayer, or Neoprontosil, Winthrop). Azosulfamide is a sodium salt of an azo compound between sulfanilamide and a hydroxynaphthaline sulfonic acid with the formula shown in Figure 1.

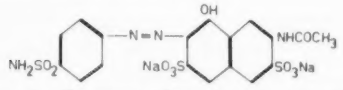

Fig. 1.—Structure formula of azosulfamide (Neoprontosil).

The supposed metabolism of azosulfamide after intramuscular injection is shown in Figure 2.

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From the Department of Clinical Biochemistry, Karolinska Sjukhuset.

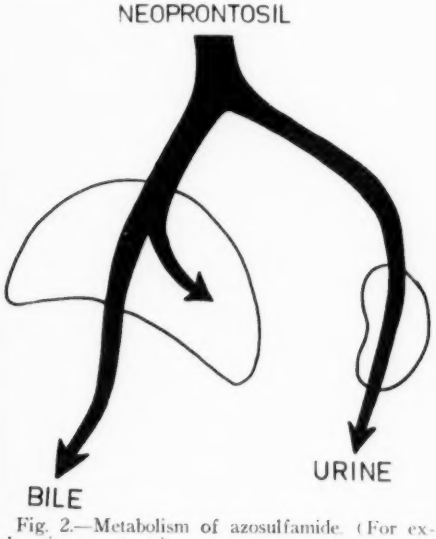

Fig. 2.—Metabolism of azosulfamide. (For explanation, see text.)

About one-half of the administered dose is taken up by the liver cells. Part of this is then excreted unchanged in the bile,[2] whereas the rest is broken down, probably by reductive enzymes.[3] One of the metabolites seems to be sulfanilamide.[4]

The remainder of the azosulfamide, i. e., the part not removed by the liver, is excreted unchanged in the urine. The elimination occurs chiefly during the first 5 to 6 hours after the injection and is completed within 24 hours. The total amount of azosulfamide eliminated in the urine gives an indirect measure of the liver function with regard to azosulfamide.

In order to evaluate the azosulfamide test as an index of liver function the following clinical investigation was carried out.

Method

The patient was given 4 ml. of a 5% aqueous solution of azosulfamide (200 mg.) intramuscularly in the morning. The urine was collected for 24 hours after the injection in vessels containing about 10 drops of an 85% (W/V) ethanolic thymol solution as preservative. The patient should be informed that the urine turns red during the test. After dilution of the urine with distilled water (suitably 1:10), the azosulfamide content was determined by measurement of the optical density in a Beckman B spectrophotometer at 500 mμ. The blank was the same diluted urine where the azosulfamide had been reduced and decolorized by adding a few crystals of sodium hydrosulfite.

The concentration of azosulfamide was obtained from a calibration curve made on solutions with known azosulfamide content.

Materials

The normal group consisted of 57 patients admitted to the hospital for check-up or for various benign disorders. They were chosen on the basis of a normal history relative to liver disease and on

normal liver-function tests. These tests included analyses of bilirubin and urobilin in the urine and direct and indirect reacting bilirubin, icterus index, alkaline phosphatase, Takata's reaction, and thymol-turbidity test in the serum.

We examined 35 patients with hepatic cirrhosis of various etiology. The diagnosis was established after thorough clinical examination during prolonged hospital observation and by the results of the ordinary liver tests. In several cases the diagnosis was confirmed by microscopical examination of liver biopsies.

We also included 27 cases of collagen disease (rheumatoid arthritis and systemic lupus erythematosus) and an additional group of patients with abnormal serum protein patterns. The latter comprised cases of multiple myeloma, metastatic cancer of the intestine, ulcerative colitis, etc.

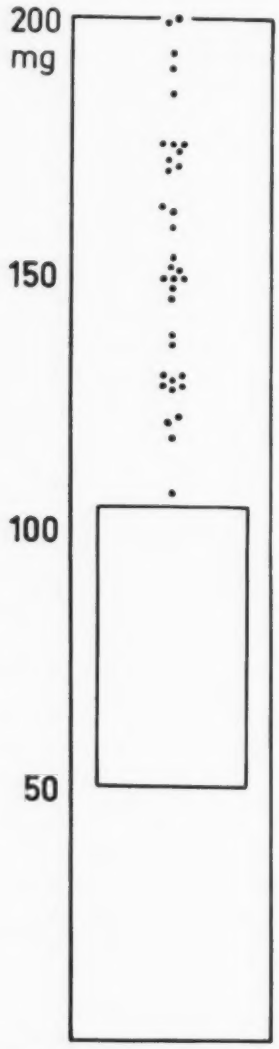

Fig. 3.—Azosulfamide excretion in 49 cases of liver cirrhosis. The small rectangle indicates the normal range. Each point represents the excretion of one case.

Results

The 57 cases in the normal group excreted from 52 to 101 mg. of azosulfamide, with a mean of 81 mg. Most of the values fell between 65 and 95 mg.; 105 mg. was regarded as the upper limit of normal excretion.

The cases with cirrhosis of the liver all showed an increased azosulfamide excretion, ranging from 107 to 200 mg. (Fig. 3). The mean was 154 mg., i. e., about twice the normal value. The test was pathological even in patients with normal ordinary tests, which is demonstrated by the following case reports:

Case 1.—A 28-year-old man, admitted for anemia and fatigue, was found to have a moderately enlarged liver. Hemoglobin was 11.8 gm. %; RBC, 3,060,000; WBC, 3,300; platelets, 106,000; icterus index, 1:10; alkaline phosphatase, 2 Buch-Buch units; thymol turbidity test, 3 units, and Takata's reaction, negative. Sulfobromophthalein (Bromsulphalein) tolerance test, normal; azosulfamide excretion on two occasions, 162 and 170 mg., respectively. The diagnosis of cirrhosis was confirmed by liver biopsy. Alcohol was the probable etiological agent.

Case 2.—A 46-year-old man, who for several years had been drinking alcohol in considerable quantities, was admitted for nosebleeds. A few days after admission he became unconscious. Treatment was started on the tentative diagnosis of hepatic coma. The liver was moderately enlarged, but the liver tests were normal (icterus index 1:6, alkaline phosphatase 5 Buch-Buch units, thymol turbidity test 3 units, and Takata's reaction negative). When the patient had recovered from the comatose state, the azosulfamide test showed an excretion of 136 mg. A liver biopsy performed a few weeks later gave the diagnosis of advanced cirrhosis.

Hypergammaglobulinemias, even those not due to liver disease, show pathological serum flocculation tests and often present a difficult problem in the differential diagnosis of hepatic diseases. Figure 4 gives the re-

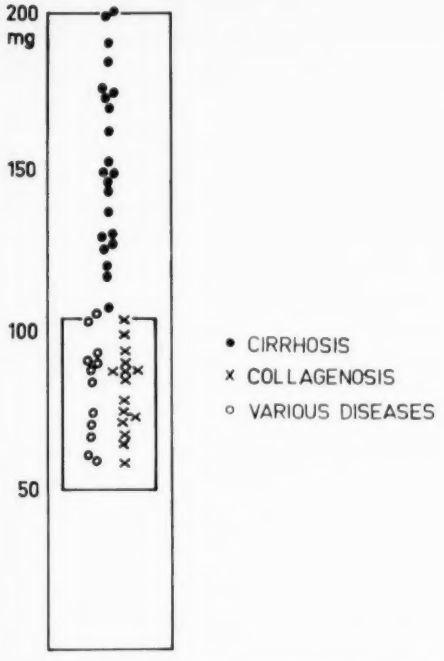

Fig. 4.—Azosulfamide excretion in 49 cases with pathological serum flocculation tests.

sults of the azosulfamide test in 49 cases with such pathological flocculation tests, i. e., Takata's reaction and the thymol turbidity test. These patients, selected at random, were apparently differentiated by the azosulfamide test into two groups, one with pathologically increased values, consisting of cases of hepatic cirrhosis, and one with normal excretion values, representing a number of cases of collagen disease and hypergammaglobulinemias of various etiology (multiple myeloma, metastatic cancer, ulcerative colitis, etc.). As the greatest part of the latter group consisted of cases of collagen disease, it seemed justified to examine a larger number of cases of rheumatoid arthritis and systemic lupus erythematosus. The excretion in 27 cases of collagen disease is shown in Figure 5. These patients had a normal excretion, though some of the values fell on the upper borderline of normal.

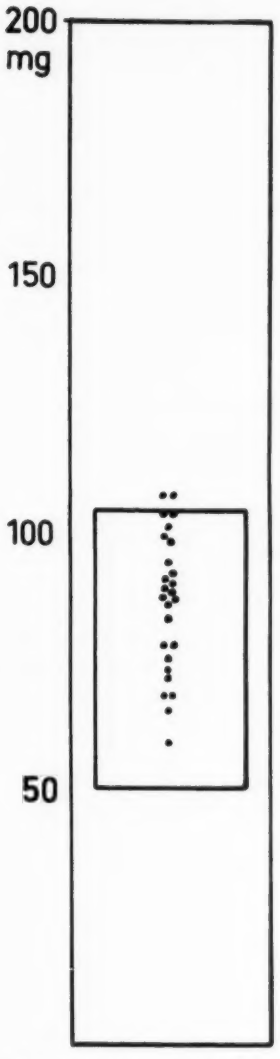

Fig. 5.—Azosulfamide excretion in 27 cases with collagen disease.

Comment

Method.—The azosulfamide test is simple and rapid, requires no venous punctures, and may be carried out in any ordinary clinical laboratory. It is also possible to use the test on outpatients.

We have not found it necessary to adjust the dose of azosulfamide in adults to the body weight as in other dye-elimination

tests. The same relative excretion was obtained after the injection of 100, 200, and 300 mg., respectively.

High bilirubin content in the urine or physiological variations of the pH of the urine did not influence the analysis. Certain bacteria, however, were able to decolorize azosulfamide in vitro, resulting in erroneously low excretion values. It was, therefore, necessary to collect the urine in vessels containing thymol to prevent bacterial growth. The bacteria capable of decolorization were found to be sulfonamide-resistant strains of Diplococcus enterococcus and Escherichia coli. The test may, therefore, be unreliable in acute purulent infections of the urinary tract.

As the azosulfamide is eliminated through the kidneys, it is apparent that an impaired renal function should give subnormal values, which has been confirmed by Siede and Schneider[5] and Hodenberg and Siemenroth.[6] We have had the same experience in some patients with renal insufficiency, and we do not consider the test applicable to cases with increased nonprotein nitrogen values.

Complications are considered to be very rare. Siede and von Schneider[5] only reported one case of allergic reaction. We have not seen any side-effects in over 500 tests.

Clinical.—The mean azosulfamide excretion of normal persons, in our material, was essentially the same as reported by Siede and Schneider[5] (81 and 85 mg., respectively).

Increased amounts of azosulfamide were excreted by all patients with cirrhosis, not only cases with pathological liver tests (bilirubin, alkaline phosphatase, and flocculation tests) but also those without any abnormality in these tests, as exemplified above. No apparent correlation could be demonstrated between azosulfamide excretion and serum bilirubin. This discrepancy may be explained when it is considered that all liver tests, including the azosulfamide, measure only a limited part of the multiple functions of the liver and that these functions may vary independently of each other.

Available data in the literature as to liver function in collagen disease are contradictory. Some authors, have found impaired glucose tolerance, abnormal azorubin S test, and abnormal sulfobromophthalein retention,[7-9] while other investigations showed normal liver-function tests.[10,11] The result of the azosulfamide test in our material of collagen disease seems to indicate an essentially normal liver function in these cases, but we consider it too early to express a definite opinion in this matter.

Siede and Schneider[5] found that the sulfobromophthalein and the azosulfamide tests were comparable as to sensitivity. Jansen[12] concluded that the azosulfamide test was as good as the azorubin S tolerance test for the evaluation of liver-function impairment. Recently Eberhard and Schmidt[13] have made a comparison of the azosulfamide test and the so-called two-dye test described by Zimmer.[14] These authors claimed that the azosulfamide test was inferior to the two-dye test. Their investigation is, however, open to criticism, as bacterial contamination may be responsible for some of their extremely low excretion values.

Summary

A liver-function test with use of the red sulfonamide compound, azosulfamide (Neoprontosil), is described. The amount of dye excreted in the urine during 24 hours after an intramuscular injection gives an indirect measure of liver function.

Normal persons excreted 65 to 95 mg. of azosulfamide (mean, 81 mg.); patients with cirrhosis of the liver, 107 to 200 mg. Most cases of collagen disease showed normal excretion.

It seems possible to use the test to differentiate between hypergammaglobulinemia of hepatic and nonhepatic origin.

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Case Reports

Chlorpromazine and Iproniazid Toxic Hepatitis in the Same Patient

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The wide diversity of usefulness of chlorpromazine * in clinical practice is too well known to review in this paper. Suffice it to say, it has found widespread acceptance because of its profound antiemetic effect, its ability to potentiate narcotics and sedatives, and most of all, its capacity to alleviate anxiety, agitation, and tension states. Dosage has varied tremendously, and complications have been noted at all dosage levels and at all durations of therapy.

We are primarily interested in the production of jaundice as a complication of chlorpromazine therapy, which has been reported in as low as 0.2% [1] and as high as 5% of patients,[2] with an average of 1.26% [3] (103 cases of jaundice in 8,127 treated cases). Histologic and biochemical data indicate a picture which mimics extrahepatic obstruction: An elevation of the serum alkaline phosphatase, serum cholesterol, and serum bilirubin, with little or no disturbance of the cephalin flocculation or thymol turbidity. Microscopically, one finds a stasis of bile in the intralobular canaliculi, with little or no inflammatory infiltration. The jaundice appears to be due to obstruction within the intrahepatic bile passages, hepatocellular function remaining unimpaired.[4]

More recently iproniazid,† a new drug related chemically to isoniazid, has been introduced to the medical profession. Because of its chemical relationship to isoniazid it was first used in the treatment of tuberculosis in relatively high dosage (300 mg. daily), where a considerable number of side-effects were noted. After this, because of its apparent ability to give a sense of euphoria or well-being, it was designated as useful in the treatment of depression and chronic diseases associated with emotional disturbances. The side-effects previously noted were apparently reduced in both incidence and severity by employing smaller doses, about 150 mg. daily in divided doses. Of late, it has been advocated as a useful adjunct in the treatment of angina pectoris in dosage of 50-150 mg. daily.[5] Medical reports are now appearing regarding its many uses, and, of course, noting many of its side-effects, which include those disturbing gastrointestinal function (constipation, flatulence), urinary function (delay in starting micturition), the locomotor system (fatigue, weakness, and lower extremity paresthesias), and the central nervous system (euphoria, somnolence, vertigo, and loss of libido). Also noted and of primary concern to us is its hepatotoxic nature, which is unpredictable as to severity and is usually associated with high dosage and prolonged therapy. The evidence here in regard to the hepatotoxic effect reveals the resulting liver involvement to be much severer, more prolonged, and more serious in nature than that associated with chlorpromazine therapy. At least one fatality is well documented, and the reports on others of fatal and nonfatal outcome are on the way. In this toxic hepatitis, not only do we find the picture of hyperbilirubinemia and elevated serum alkaline phosphatase but there are evidences

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* Thorazine, Smith, Kline & French Laboratories.

† Marsilid, Hoffmann-LaRoche, Inc.

of cellular damage in the positive cephalin flocculation, increased thymol turbidity, and markedly increased serum glutamic pyruvic transaminase (SGPT) activity. With chlorpromazine hyperbilirubinemia the SGPT is usually greater than the serum glutamic oxalacetic transaminase (SGOT) activity, ranging from 68-72 units in the latter and 176-300 units in the former.[6] With iproniazid the transaminase activity is frequently over 1,000 units, with the SGOT greater than the SGPT activity.

Biopsy and autopsy findings of livers affected by iproniazid are indistinguishable from acute viral hepatitis.[7] Pharmacologic studies reveal that iproniazid is a potent inhibitor of amine oxidase, a liver enzyme, which could account for not only the activity but also part of the toxicity of the drug.[8] In all species of animals it has demonstrated evidences of cumulative toxicity.[9]

The function of this liver enzyme is the removal of biological amines from the body and the prevention of accumulation of these potentially toxic amines in excessive amounts. In addition, these liver enzymes which are inhibited have the function of detoxifying various drugs.

We feel that this case is of unusual medical interest, because it represents a unique situation in that the same person developed a drug-induced hepatotoxic jaundice two times within an interval of two years. The two drugs are markedly dissimilar in structural formula but are used for the same indications by many physicians (especially the psychiatrists) because of their particular value in the treatment of emotional disturbances.

Report of Case

A 31-year-old white woman was first seen on Nov. 13, 1955, at home, complaining of epigastric fullness, anorexia, nausea, and nonspecific malaise. She was afebrile and apparently without jaundice. A diagnosis of probable gastritis was made, and antacid and antispasmodic therapy was prescribed. She was seen again on Nov. 15, 1955, at which time she was visibly icteric, had tenderness and pain over the right upper quadrant, was afebrile, and noted dark urine and lightened stools. Subjectively she felt worse. Blood studies revealed a normal hemogram, without eosinophilia; serum bilirubin, 2.4 mg. %; cholesterol, 210 mg. %, and cephalin flocculation, 1+ in 24 hours. History now revealed the ingestion of three 25 mg. tablets of chlorpromazine on Nov. 15, which were prescribed by her psychiatrist for a feeling of depression. She had taken none after that date. She made a rapid recovery at home on a routine of bed rest and a high-protein, high-carbohydrate, and low-fat diet. On Dec. 3, no jaundice was apparent; stool and urine were normal; serum bilirubin was 0.35 mg. %, and the cephalin flocculation was negative. Subjectively she still had vague abdominal complaints. A diagnosis of toxic hepatitis due to chlorpromazine was made. Subsequent gallbladder visualization was reported normal. In February, 1956, and May, 1957, repeat blood studies, including bilirubin and cephalin flocculation, were done and found to be normal.

On Feb. 17, 1958, the patient was seen in the office, complaining of upper abdominal pain, nausea, anorexia, weakness, and generalized malaise. Her temperature was 100 F, and she was obviously jaundiced, with dark urine (positive for bile) and normal-looking stools. History revealed that the patient had again been treated by her psychiatrist for a depression and was taking iproniazid, 50 mg. three or four times a day for two months. She had noted constipation and somnolence on this therapy but appreciated a definite increased sense of well-being. Laboratory data now revealed a serum bilirubin of 3.15 mg. per 100 ml. of blood; cholesterol, 153 mg.; cephalin flocculation, 2+ in 24 hours and 3+ in 48 hours; hemogram, normal, without eosinophilia.

Treatment was attempted at home, but because of her extreme discomfort, pain, nausea, and anorexia she was admitted to the Newark Beth Israel Hospital for treatment, on Feb. 25, 1958. Laboratory data on Feb. 26, 1958, revealed hemogram, normal; L. E. preparation, negative; circulating eosinophils, 967 per cubic millimeter; bleeding time, 4 minutes; urinalysis, negative for urobilinogen and positive for bile. Blood studies, while she was hospitalized from Feb. 26, 1958, through March 17, 1958, showed repeated normal blood sugar, blood urea nitrogen, and hemogram. Urines were also normal, except for the presence of bile. The serum bilirubin on admission was 7.4 mg. %, rising to 13.5 mg. % on Feb. 28, 1958, and gradually declining to 0.9 mg. % on March 17, 1958. The alkaline phosphatase varied between 3.4 and 5.9 Bodansky units. The albumin and globulin ratios were inverted at the beginning, returning to a 1:1 ratio at the time of discharge. Cephalin flocculation was 4+ on admission and 2+ on discharge. The SGOT activity was 460 units and the SGPT activity, 980 units on admission, dropping to 84 and 380 units, respectively, at the time of discharge. Heterophil antibody, cold

agglutinins, and febrile agglutinins were all normal, as were biliary drainage, guaiac stool test, and stool urobilin.

Her course in the hospital was not unusually stormy, although she required parenteral fluids the first few days and was treated with oral steroids in conjunction with the usual bed rest and indicated diet. When discharged, on March 18, 1958, she was no longer jaundiced but still had abdominal distress and weakness. Modified bed rest was continued at home and gradually diminished until April 12, 1958, when a complete restudy of the liver function revealed all was normal except for a 1+ cephalin flocculation. Biopsy of the liver was not performed or attempted.

Comment

It would seem apparent from the medical literature that we have available to us an increasing number of drugs, useful in many ways but frequently capable of resulting in complications perhaps more serious or disabling than the condition being treated. Chlorpromazine therapy, it is reported, can be reinstituted in the same patient after the jaundice has disappeared, without danger of relapse, and patients have recovered from jaundice while the drug was continued.[3] One wonders, however, why such a chance or procedure should be undertaken. With iproniazid we are confronted with a known hepatotoxic agent, cumulatively toxic and productive in susceptible patients of a severe, perhaps fatal condition. When and if we decide that the risk involved is small or insignificant as compared to the therapeutic effect we anticipate and when we feel that there is no adequate less toxic substitute, we may then take a "calculated risk." In this case we have a patient extremely sensitive to a hepatotoxic agent (chlorpromazine) who subsequently was given a much more hepatotoxic agent (iproniazid). Certainly, if one is aware of such a previous history, should one reexpose the patient to another toxic compound, without considering the increased likelihood of another untoward reaction? We think not.

Summary and Conclusions

A case of toxic hepatitis produced by chlorpromazine and later by iproniazid in the same patient is reported.

The jaundice occurred after one day of therapy with the chlorpromazine and after two months of therapy with the iproniazid. The patient recovered completely from both episodes.

The jaundice produced by the chlorpromazine was associated with intrahepatic biliary stasis and obstruction, without evidences of hepatocellular damage; while that produced by the iproniazid was indistinguishable from severe acute viral hepatitis.

Because of the serious nature of hepatic reactions, hepatotoxic drugs should not be used promiscuously and should be reserved for those conditions where the benefits of the drugs far outweigh the risks.

Patients previously discovered to be susceptible to a hepatotoxic substance should not be exposed unnecessarily to another such toxin, regardless of the dissimilarity of the chemical relationship existing between the two.

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Phenylbutazone Leukopenia

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While effective in a variety of rheumatic conditions, phenylbutazone has incurred the reputation of being a relatively toxic drug. Purpura,[1] depression of erythropoiesis,[2] aggravation of bleeding ulcers,[1] and Stevens-Johnson syndrome[3] have been reported consequent to its administration, but by far the most alarming complications of phenylbutazone therapy have been agranulocytosis and, more frequently, leukopenia.[1] The nature of white cell damage produce by this agent has not been previously elucidated, although structural similarities to aminopyrine have caused speculation as to analogous leukotoxicity.

Certain drugs, when added to the serum of patients with leukopenia, will cause agglutination of autologous and homologous white blood cells. Gold and aminopyrine particularly have been mentioned in this regard.[4] It is the purpose of this communication to add phenylbutazone to this list and to examine the relationship that the drug bears to aminopyrine in leukoagglutination activity. We have studied a patient whose serum caused agglutination of homologous white blood cells when incubated with phenylbutazone or with aminopyrine. The agglutinating factor in serum was present at a time when the patient clinically had a leukopenia consequent to phenylbutazone therapy. One month after clinical recovery, no such reactions could be demonstrated.

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Report of Case

A 35-year-old Negro porter was admitted to The Mount Sinai Hospital on April 16, 1958, for evaluation of hypertension and right ankle pain.

The patient had been known to suffer from hypertension since December, 1955. He presented himself to his physician with frontal headache, and blood pressure readings of 170/100 were recorded. He was treated with reserpine with moderate symptomatic relief. Because of repeated headaches he was next seen as an outpatient at another hospital where an intravenous urogram was performed. In the arm used for injection of the dye thrombophlebitis developed, and he was admitted for treatment on Dec. 16, 1957. At that time the blood urea nitrogen was 8 mg. % and the white blood cell count was 7,200, with a "normal differential count." The thrombophlebitis responded well to simple treatment.

From Jan. 29, 1958, to April 3, 1958, the patient was treated for his hypertension with hydralazine in dosages of 150 to 250 mg. a day. During this time he developed arthralgias and swellings of both legs, together with shoulder pains. No true arthritis was noted. Because of these musculoskeletal complaints the patient was given phenylbutazone, 400 mg. a day, which was continued to April 12.

No history of allergy was elicited. In January 1957, the patient had pneumonia of his right lower lobe and transient thrombophlebitis of the right leg. In March 1949, the patient was treated for cellulitis of the left leg. In 1944, the patient was treated with penicillin for syphilis. Recent Wassermann tests had been negative.

Physical examination revealed a stocky Negro man in no distress save for right ankle pain. The temperature was 99.8 F; pulse, 72, and respirations, 20. Positive physical findings included the presence of some heat and swelling of the right ankle and arterial hypertension of 160/100. The eyegrounds showed early nicking of the veins by arteries. A faint systolic murmur was audible over the precordium. The remainder of the physical examination was unremarkable.

The urine was clear and yellow, had no significant sediment, and gave negative reactions for protein, acetone, and sugar. The hemoglobin varied between 12 and 13 gm. %, while the white blood cell count varied between 2,500 and 3,700

TABLE 1.—*White Blood Cell Counts in Patient with Leukopenia Presumably Due to Phenylbutazone*

Date, 1958	WBC	Polymorph. Segmented	Bands	Lymph.	Eos.	Mono.
		"Normal differential"				
2/3	7,200					
4/16	3,900	64	5	16	6	9
4/18	2,500	60	2	28	7	3
4/22	3,150	54	4	21	11	10
4/25	3,750					
4/28	3,100	63	5	21	5	6
5/3	7,100	70	5	11	3	6
5/19	7,150	69	5	22	2	2
6/23	7,200	60	4	32	3	1

cells per cubic millimeter (Table 1). There were from 6% to 11% eosinophils; the remainder of the differential count was normal. The platelets were 125,000 cells per cubic millimeter. The sedimentation rate was 35 mm. in the first hour (Westergren). The blood urea nitrogen was 16 mg. %; the glucose, 93 mg. %; the albumin, 3.9 gm. %, and the globulin, 3.6 gm. %. The cholesterol was 230 mg. %; the alkaline phosphatase, 5.1 King-Armstrong units; the uric acid, 5.1 mg. %, and the creatinine 1.3 mg. %. The thymol turbidity was less than one unit, and the glutamic-oxalacetic transaminase was 10 Karmen units. Stools were negative for occult blood, and no ova or parasites were found. The urine could be concentrated to a specific gravity of 1.020. The creatinine clearance was 120 ml. per minute (normal). The C-reactive protein test was never positive, and the antistreptolysin titer was less than 110 on several occasions. Only hemoglobin A was present on paper electrophoresis. Serum electrophoresis showed only minimal increase in γ-globulin, with a diminution of the α_2-globulin. The latex-fixation test for rheumatoid arthritis was negative, as were Wassermann, Kahn, and Mazzini tests. Several lupus erythematosus preparations were negative. Serum globulin fractionation indicated the normal values of 70 mg. % mucoproteins, 3.2 units of acid-precipitable globulin, and 5 units of zinc sulfate turbidity. The second-strength-tuberculin and Frei tests were both positive. Roentgen examinations of the gastrointestinal tract, urogenital tract, both ankles, and the thorax were within normal limits. A phentolamine (Regitine) test for pheochromocytoma was negative. Electrocardiograms showed minor T-wave inversions in Leads II, and III and aV_F. A skin and muscle biopsy specimen was reported as showing only "normal tissue, with no evidence of arteritis." Examination of the bone marrow showed depression of the myeloid series, with a slight increase of eosinophils but with normal erythroid series and adequate megakaryocytes.

The patient was placed at bed rest while the above examinations were performed. His blood pressure varied between 160/100 and 150/90. An episode of cellulitis followed the muscle biopsy, and concurrently with this infection the initial leukopenia disappeared. The white cell count rose to 7,200 but never above this figure. When the history of drug intake was elicited, efforts were made to determine the effects of the patient's serum and phenylbutazone upon normal white blood cells. It seemed probable that the patient was suffering from essential hypertension. The various joint symptoms were ascribed to hydralazine toxicity, and the leukopenia could satisfactorily be explained by the toxic effect of phenylbutazone. After several weeks without any therapy, all symptoms cleared and the blood cell count returned to normal.

Studies of Leukoagglutination.—Serum from the patient, taken at a time when the white cell count was 2,500 cells per cubic milliliter, was studied for leukoagglutinin activity. The technique of Dausset[6] was used throughout. Leukocytes were obtained from a type-compatible donor to rule out red cell agglutination (O-positive). Blood was defibrinated by gentle agitation in small Erlenmeyer flasks containing glass balls 4 or 5 mm. in diameter. This served to remove platelets as well as fibrin. One-fifth of the original volume of 6% dextran was added to accelerate normal sedimentation. The blood was permitted to sediment for one-half hour at 37 C in tubes inclined at an angle of 45 degrees. Leukocyte suspension, in the amount of 0.10 ml., thus obtained was added to 0.10 ml. of the patient's serum after this had been heated at 56 C for 30 minutes. Solutions, 0.02% W/V of aminopyrine, phenylbutazone, and five phenylbutazone analogues * were prepared. Drug solution, 0.10 ml., was next added to the system; the tubes were agitated and placed in the incubator at 37 C for one hour and

* G-25671, G-28315, Metabolite 1, G-12838, and G-25921 were supplied by Dr. T. F. Yü.

TABLE 2.—*Leukoagglutinins (Technique of Dausset) Demonstrated with Serum of Leukopenic Patient and Several Drugs*

Drug, 0.02% Solution	Serum	WBC, O-Positive Donor	Result-Titer, Furthest Dilution with Positive Agglutination
Phenylbutazone		Normal	0
Phenylbutazone	Patient	Normal	1:64
Phenylbutazone	Normal	Normal	0
Aminopyrine		Normal	0
Aminopyrine	Patient	Normal	1:64
Aminopyrine	Normal	Normal	0
Metabolite 1		Normal	0
Metabolite 1	Patient	Normal	1:32
Metabolite 1	Normal	Normal	0

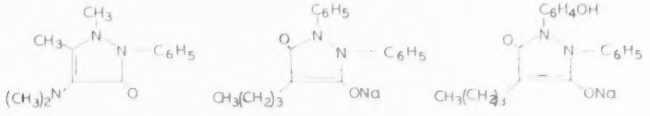
read immediately. The grading of leukoagglutination was according to Dausset: negative, 1+, 2+, 3+, and 4+.

The results are indicated in Table 2 for phenylbutazone, aminopyrine, and Metabolite 1,[6] a recently studied metabolite of phenylbutazone with hydroxyl group substitution on a phenyl ring. Four other phenylbutazone derivatives were found to show similar titers. To rule out a possible agglutination effect of the drugs themselves, 0.3% W/V solutions of the test drugs were added to white cell suspensions and no agglutination was noted. The serum of the patient alone did not agglutinate white cells. The 0.02% solutions approximated therapeutic dosage. Serial dilutions of the serum were carried out in an attempt at rough quantitation. Aminopyrine and phenylbutazone both gave definite 1+ agglutination at 1:64 serum dilutions, while Metabolite 1 gave this reading at titers to 1:32. When serum was tested for similar activity one month after the patient's discharge and at a time when the white cell count was normal, no leukoagglutination could be demonstrated with any drug.

Comment

The toxic effects attributable to phenylbutazone are many, but the greatest hazard associated with the use of this drug has been leukopenia. In 1955, Mauer [1] reported 23 deaths directly due to the drug, and there have been several since. In a review of reports concerning 3,934 patients, he noted 6 cases of agranulocytosis and 34 of leukopenia. Yet when single case reports were analyzed, he discovered that 15 of 19 patients were described with agranulocytosis, and 10 of these 19 cases terminated fatally. The leukopenia is not directly related either to the length of drug administration or to the dosage. Indeed, leukopenia can develop shortly after discontinuance of the drug. This is borne out by the study of Bruck et al.,[7] who were able to detect phenylbutazone in concentrations of 15 mg. per liter in serum 8 days after therapeutic dosage and traces of the drug 10-21 days after treatment. The frequent depression of the white cell count by this drug has even caused investigations into a possible antileukemic activity. Thus a search for the role played by phenylbutazone, its derivatives, and its congener aminopyrine in the agglutination of normal white cells by phenylbutazone-sensitive serum was undertaken. It seemed of interest that the phenylbutazone derivatives, whether substituted on the phenyl ring or in the butyl side-chain, continued to show leukotoxic effect. The cross reaction of aminopyrine and phenylbutazone in this system is of evident practical import. The linkage $R(C_6H_5)N—N—CO—R$ may be a determinant, as shown in the Figure.

Following the demonstration that immunological mechanisms could produce thrombocytopenia and anemia,[8] many investigators have tried to implicate similar mechanisms in leukopenia and agranulocytosis.[4,9] Dameshek and Colmes [10] demonstrated skin sensitivity to aminopyrine in four patients with granulocytopenia presumably due to that drug. Of interest was the markedly enhanced hypersensitivity they observed to suspensions of serum *and* the offending drug. Moeschlin and Wagner [11] transfused blood from an aminopyrine-sensitive patient into a normal subject and observed granulocytopenia 20-40 minutes after such transfusion. They were also able to demonstrate in vitro agglutination of autologous and homologous leukocytes by the serum of an aminopyrine-sensitive person while he was receiving the drug. While aminopyrine itself produced no direct agglutination of the patient's white cells, after incubation with patient's serum it produced agglutination not only of the patient's cells but of normal cells as well. Since then, such reactions have



AMINOPYRINE PHENYLBUTAZONE METABOLITE 1

been confirmed by Benhamou et al.[12] and Tullis.[4] Methods used to demonstrate such antileukocyte factors have been many and seem open to serious criticism. The agglutination of cell suspensions, the depression of phagocytosis, and the counting of normal cells in a known suspension before and after the addition of test serum have all been employed to evaluate anti-white-cell substances.

The demonstration of leukoagglutinin activity in serum need not imply sensitivity of the patient to drugs alone. Patients with lymphomas, carcinomas, hypersplenism, and a variety of conditions characterized by leukopenia may have such agglutinin activity demonstrable in whole serum.[5,9,13] It is the enhancement of such activity by addition of the drug itself that seems of particular import. Tullis[4] divides the leukopenias attributable to drug sensitivity into two classes. In patients with hypercellular bone marrow and a relative "maturation arrest," he was able to demonstrate leukotoxic activity in 10 of 18 sera. Patients who manifested an aplastic marrow never had leukotoxic activity in their serum. This author again demonstrated that the addition of gold to a suspension of a gold-sensitive patient's serum and normal white cells augmented leukotoxic activity. The factor causing such activity in serum was partially isolated in the α- and the β-globulin fractions of serum but could not be characterized any further. Most observers believe that the various drugs behave as simple haptenes in provoking an antibody response to the drug-patient's serum protein complex. Yet in white cell agglutination studies, such a hypothesis has not yet been established to the degree that it has in the experiments with drug-induced purpura.[8] Why the antibodies, if indeed the factors in serum are antibodies, are directed against white cells and not against other blood elements is a question that remains to be answered. The demonstration of cross reactivity in the induction of leukoagglutination between various phenylbutazone analogues and aminopyrine itself seems to bear further study. The particular chemical bonding responsible for the induction of such leukoagglutination also deserves more careful consideration. It is of significance that two months after the patient's discharge from this hospital the white cell count was normal and no leukoagglutination could be produced by the patient's serum with any of the drugs tested. This would indicate that the serum factor is present in blood only in close relationship to drug administration. Presumably then, genetically transmitted enzyme defects may not play a role in this phenomenon.

Summary

Leukopenia, presumably due to phenylbutazone toxicity, was present in a 35-year-old Negro man. The serum of this patient, when incubated with dilute solutions of phenylbutazone, caused agglutination of normal white cells. Neither serum nor phenylbutazone alone was able to produce such agglutination. Similar reactions were demonstrable with the same patient's serum and aminopyrine, as well as several other phenylbutazone analogues. The implications of these findings in terms of the granulocytopenia frequently seen after the use of such drugs are discussed. It is suggested that phenylbutazone functions as a haptene in the production of antileukocyte antibodies.

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Aortic Arch Syndrome

A Report of an Unusual Surgical Complication

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In recent years the syndrome of occlusive disease of the major vessels of the aortic arch has appeared with great frequency in the medical literature.[1-8] We wish to add the following case, which is unusual because of its surgical complication.

Report of Case

This was the fourth Coral Gables Veterans Administration Hospital admission for this 46-year-old white, married man who presented with the chief complaint of loss of vision in the right eye of 72-hour duration.

The patient's present illness began while in the Armed Forces when, at the age of 32, he was hospitalized (March, 1945) for intermittent claudications of both calves associated with easy fatigability. Examination at that time revealed loss of all pulsations below the femorals bilaterally and a markedly diminished left femoral pulsation. The blood pressure was 122/72; no mention was made of carotid or radial pulses. X-ray examination of the abdomen revealed moderate calcification of the lower abdominal aorta. The total serum cholesterol was 220 mg. %; other studies, including glucose tolerance, electrocardiogram, chest x-ray, and serology, were unremarkable.

After discharge from the service, the patient continued to have intermittent claudication until July, 1947, when he was first admitted to this Veterans Administration Hospital with severe substernal and precordial pain radiating down his left arm. Physical examination at that time revealed a blood pressure of 200/120. A Grade 3 high-pitched apical systolic murmur and markedly diminished arterial pulsations in the lower extremities were observed. Unfortunately there was no mention of the character of the carotid or radial pulses. The electrocardiogram revealed an acute anterior myocardial infarction. The patient made an uneventful recovery, with a blood pressure of 140/80 recorded prior to discharge.

In September, 1949, the patient was again admitted to the Veterans Administration Hospital because of substernal pressure radiating down both arms, accompanied by a moderate degree of dyspnea. Physical examination revealed a blood pressure of 120/75, a loud apical systolic murmur, and diminished to absent pulsations in the lower extremities. No mention of carotid or radial pulses was recorded. The total serum cholesterol was 345 mg. %. Serial electrocardiograms showed an acute posterior, subendocardial, myocardial infarction. With anticoagulants and other standard therapeutic measures, the patient experienced an uncomplicated convalescence.

In December, 1951, he was again admitted to the hospital because of acute congestive heart failure. For the first time, a rumbling diastolic mitral murmur with presystolic accentuation as well as a blowing mitral systolic murmur were heard. There was no history or physical findings to suggest active rheumatic fever. Cardiac fluoroscopy revealed left auricular and right ventricular enlargement. Electrocardiograms showed residual changes of the previous infarctions. There was again no record of examination of the peripheral pulses. With bed rest, diet, and digitalis the patient progressively improved and was discharged relatively asymptomatic. At no time during this hospitalization was hypertension recorded.

In September, 1953, the patient was readmitted because of sudden loss of vision in the right eye, lasting approximately three minutes, with apparent complete recovery. For several weeks prior to this the patient had noted transient paresthesias in the left arm and left leg. Physical examination revealed moderate arteriosclerotic changes in the optic fundi with a single small hemorrhage in the right fundus. The blood pressure was recorded as 140/100. No change was observed on examination of the heart and peripheral vessels. The patient became asymptomatic and was discharged shortly after admission.

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From 1953 to July, 1957, the patient had enjoyed relatively good health except for intermittent claudication and rare episodes of angina pectoris until the sudden loss of vision in his right eye 72 hours prior to his present admission. Eighteen hours after admission some degree of visual acuity returned, but there was an apparent inferior nasal field defect. Physical examination revealed a blood pressure of 86/64 in the right leg, temperature of 96 F (oral), and pulse of 82 per minute and regular. The patient was 62 in. tall and weighed 106 lb. A crusting scaling 2.0 cm. lesion with rolled edges was observed on the left side of the forehead in an area of an old scar. There were no radial pulses, and no blood pressure could be obtained in either upper extremity. The right carotid pulse could not be palpated, and only an extremely faint pulsation was felt in the area of the left carotid. There were, however, loud systolic bruits auscultated over the areas of both carotids. The right posterior tibial and left anterior tibial arteries were weakly palpable. The other pedal pulses and popliteal pulses were absent. The left femoral pulse was markedly diminished, while the right femoral was moderately decreased. Loud bruits were heard over both of these vessels. Examination of the optic fundi revealed Grade II arteriosclerotic changes. No hemorrhages or exudates were noted. Visual field examination confirmed the presence of a partial nasal field defect in the right eye. The heart appeared slightly enlarged, with the point of maximal impulse being 2 cm. outside the midclavicular line in the fifth intercostal space. The murmurs of mitral insufficiency and mitral stenosis were easily audible. The remainder of the examination was unremarkable.

The electrocardiogram was suggestive of left ventricular hypertrophy and an old posterior wall subendocardial infarction. Fluoroscopy revealed left auricular and moderate biventricular enlargement. An aortogram failed to visualize the lower abdominal aorta or iliac vessels. An intravenous pyelogram was within normal limits. A skeletal muscle biopsy showed no abnormalities of the smaller blood vessels. The radioactive iodine uptake and serum electrophoretic pattern were normal. In essence, the only abnormalities noted in a thorough biochemical and hematological evaluation were a total serum cholesterol of 445 mg. % and an elevated blood urea nitrogen of 34 mg. %, with a creatinine of 1.8 mg. %. The phenolsulfonphthalein excretion was 10% in the first 15 minutes; a maximum urinary concentration of 1.018 was observed. Skull films, electroencephalogram, and lumbar puncture were normal.

The patient was placed on anticoagulants and continued on maintenance digitalis. After four weeks of hospitalization, there was only a minimal residual defect in the visual fields. No change in the patient's cardiovascular system was noted. Further study to determine whether the patient's illness represented a so-called "collagen disease" rather than diffuse arteriosclerosis was undertaken. Except for additional evidence of moderate impairment in renal function, there was nothing to substantiate such a diagnosis.

A dermatological consultation was obtained because of the skin lesion on the patient's forehead. This was considered to be a typical basal-cell carcinoma. Anticoagulant therapy was stopped and under local anesthesia the skin lesion was excised. Microscopic examination confirmed the clinical impression of a basal-cell carcinoma. It was observed at the time of surgery that bleeding was minimal.

Postoperatively the wound failed to heal, and there was necrosis of the suture line. Accordingly, a flap repair of the postoperative defect was done. In spite of careful postoperative care, the flap sloughed and a large defect remained.

A split-thickness skin graft from the left thigh to the forehead was the next surgical procedure. At this procedure the paucity of operative bleeding was again recorded.

In the following six months the patient had three split-thickness grafts from his thigh and an excision skin graft. In spite of careful postoperative care by competent plastic surgeons and neurosurgeons, all operative procedures have failed to close the defect and frontal bone osteomyelitis has developed. At the present time, the large defect appears to be slowly granulating (Figs. 1 and 2). It is doubtful that additional surgery will be successful because of the extremely poor blood supply. There has been no change in the patient's cardiovascular status.

Fig. 1.—Area of basal-cell carcinoma after multiple excisions.

Fig. 2.—Area of flap, showing failure of healing.

Comment

Previously described, in 1908, by a Japanese ophthalmologist, Takayasu,[9] as a rare disease afflicting young females, the concept of aortic arch syndrome, or "pulseless disease," has been broadened to include cases in both sexes and in the older age group. Initially, tuberculosis and syphilis were believed to be the etiological agents of the arteritis that occluded the major vessels of the aortic arch. The current concept is one of a multiplicity of causes, including atherosclerosis, healed aneurysms, necrotizing angitis, trauma, giant-cell arteritis, and thrombophilia.

Ross and McKusick,[2] in a review of over 100 cases, failed to find any single major cause for this syndrome. Burstein and coworkers,[7] in a careful review of five cases, believed that atherosclerosis was a more important etiological cause than had been previously reported in the literature. With an apparently increasing incidence of atherosclerosis in an aging population, it appears that this syndrome will be more commonly encountered in the years to come.

The symptoms of occlusive disease involving the major vessels of the aortic arch can be divided into four major categories:

1. *Visual Disturbances.*—These were the first symptoms noted in the original description of "pulseless disease." They include optic atrophy, transient loss of vision, diplopia, cataracts, and corneal dystrophies.

2. *Central Nervous System Disturbances.* These include dizziness, vertigo, headaches, aphasia, convulsions, mental impairment, and transient hemiparesis and hemiplegia.

3. *Ischemia of Upper Extremities.*—These have been minimized and never as severe as the disturbances due to optic or central nervous system ischemia. Symptoms include intermittent claudication and trophic changes. Amputation has not been recorded.

4. *Ischemia of Facial Structure.*—These include atrophy of the facial skin and ischemia ulceration of the nasal septum and surrounding structures.

As more and more cases of the aortic arch syndrome are reported, it is becoming apparent that this entity is not the rarity that it was once considered. In light of the rapid advances in surgical technique, major surgery has been attempted in an effort to eliminate obstruction of the innominate, subclavian, and carotid arteries.[10,11] The role of anticoagulants has not been fully evaluated, but promising results have been reported.[1,2,7,12] Because of the possibility that this might represent an arteritis of the collagen-like family of diseases, steroids with and without anticoagulants have also been used, with somewhat inconsistent results.[7]

The etiology in our case is not clear. The patient showed evidence of occlusive disease of vessels other than those of the aortic arch. The past history of myocardial infarction and the association of hypercholesteremia, in addition to evidence of involvement of the femoral arteries, appear to make atherosclerosis the most likely etiology. The possibility of a diffuse angiitis was considered in view of the history of hypertension. The negative muscle biopsy, the lack of progressive renal impairment, the lack of evidence of hepatic or gastrointestinal involvement, and the slow progression of symptoms suggest that this is not a periarteritis-like picture. The relationship of severe mitral valvular disease to the diffuse arterial disease is also not clear. The etiological posibility of multiple emboli

to the major aortic branches appears extremely unlikely. There was no historical or laboratory evidence of syphilis or tuberculosis, and there was no history of trauma.

The serious complications following an apparently minor surgical procedure warrant comment. The lesion had the typical appearance of a basal-cell carcinoma and had been growing slowly (according to the patient). There were no obvious signs of ischemia of the facial structures, and the scalp is well known for its amazing recuperative powers. However, in spite of good surgical technique, multiple skin grafts have failed to take and the defect has progressively enlarged. A relatively bloodless field was observed during the surgery. In retrospect, it now appears that the tumor might very well have outgrown its blood supply and perhaps would never have presented a serious threat to the patient's health.

This case is reported to stress the value of completely assessing the blood supply to the head and neck in patients in all age groups prior to a surgical procedure, however small. Even in instances of neoplasia, where the carotid circulation is severely compromised, a conservative, cautious approach by the internist and surgeon would appear desirable.

Summary

A case of the aortic arch syndrome is presented in a patient with evidence of diffuse arterial occlusive disease. The possible etiology is discussed, and the disastrous results of apparently minor facial surgery are emphasized. The necessity for careful evaluation of the circulation prior to surgery in patients with evidence of severe occlusive disease of the major branches of the aorta is stressed.

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Eosinophilic Granuloma of Lung

Clinical Features and Connective Tissue Patterns

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Eosinophilic granuloma may be defined briefly as a chronic inflammatory disorder of unknown etiology characterized primarily by the presence of histiocytes and eosinophils. General awareness of this disease may be said to be a consequence of two almost simultaneous but independent studies which appeared in 1940,[1,2] although Mazzitello[3] mentions the existence of less well-appreciated earlier descriptions. After 1940 a series of papers appeared in considerable number, and a clinical and pathological spectrum has gradually evolved.

Histologically, many of the cases have shown apparent transitions with two other disorders, namely, the Hand-Schüller-Christian syndrome and Letterer-Siwe disease. So consistent have these similarities been that it is now generally conceded that all three diseases represent variants or interrelated expressions of the same fundamental malady. The over-all group has been designated as "Histiocytosis X" by Lichtenstein,[4] histiocytosis referring to the common cell type or histological hallmark and X indicating the need for identification of an etiologic agent.

Although initial studies on eosinophilic granuloma emphasized bony invasion, it subsequently became apparent that it can involve a variety of other systems, e. g., skin,[5] vulva,[6] gastrointestinal tract,[7] and lungs. This study is concerned with pulmonary eosinophilic granuloma.

Auld[8] has recently reviewed eosinophilic granuloma of the lung, and reference can be made to his work for details of the 13 histologically proven cases which he accumulated from the medical literature and his own experience. Eight of these patients presumably had the lung as the only known site of involvement; four had associated bony lesions, and one had diabetes insipidus. In another study, Thompson, Buechner, and Fishman[9] were able to collect 39 cases with pulmonary involvement, 14 of which were proven by histological study of lung tissue. The diagnosis in the remainder was dependent on biopsy of skeletal lesions or other organs associated with roentgenographic evidence of pulmonary involvement. Five of their collected series plus an additional case of their own had eosinophilic granuloma limited to the lungs, but they were aware of the possible existence of undetected extrapulmonary sites.

During the course of a current study of the histochemical features of different types of pulmonary fibrosis, we have encountered two examples of eosinophilic granuloma of the lung. Certain aspects of these two cases, such as the severity of the symptoms, the gratifying response to steroids, and the observations on the connective tissue alterations seem to be of additional interest.

Clinical Characteristics

It has been emphasized that eosinophilic granuloma of the lung is associated with a mild clinical picture.[8] The onset has been

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From the Research Laboratory, Baptist Memorial Hospital, and the Departments of Medicine, Duval Medical Center and St. Vincent's Hospital.

characterized as insidious, and symptoms have consisted chiefly of slight cough, chest discomfort, and dyspnea. The most alarming feature has been the not infrequent occurrence of pneumothorax in cases complicated by cyst formation. In contrast, our two cases, neither of which had pneumothorax, had severe respiratory insufficiency and were critically ill.

A few rales have been the commonest physical finding except in the presence of pneumothorax.[8] Lymphadenopathy and hepatosplenomegaly have been conspicuously absent despite the fact that eosinophilic granuloma represents a form of reticuloendothelial hyperplasia.

The most frequent roentgenologic finding has been a striking, diffuse reticulonodular infiltration of the lungs.[8] These shadows are of a nonspecific nature and are indistinguishable from changes that can occur with a large number of other disorders. Small cyst-like cavities or air spaces are frequently interspersed between the solid foci to produce a honeycomb appearance (fibrocystic disease).[10] If we bear in mind the circumscribed lesions that are observed in bones, the occurrence of localized pulmonary foci would be expected with some frequency. The solitary xanthoma reported by Scott and co-workers [11] had some of the characteristics of eosinophilic granuloma; however, a survey of the literature suggests that diffuse, bilateral nodular infiltrations are much commoner.

A large number of other diseases can present clinically indistinguishable findings. Some of those more commonly requiring differentiation include sarcoidosis, tuberculosis, pneumoconiosis, lymphangitic carcinomatosis, lymphoma, leukemia, the Hamman-Rich syndrome, collagen diseases, bronchiolar carcinoma, and the pulmonary mycoses. Conventional methods should, of course, be exhausted in an effort to establish an etiology in such situations, but the results are frequently disappointing in disease confined to the pulmonary interstitium. The diagnosis of pulmonary eosinophilic granuloma is dependent on histological study of diseased tissue (lung biopsy or autopsy).

Previously reported patients with eosinophilic granuloma of the lung have generally done well symptomatically with or without therapeutic attempts,[8] but it has already been noted that most had few symptoms at the outset. From an objective viewpoint, varying degrees of radiographic clearing have been observed in those cases that received roentgen therapy or adrenal steroids. Steroids appeared life-saving in our two patients, both of whom were critically ill with respiratory insufficiency.

Report of Cases

CASE 1.—A 30-year-old white housewife was admitted to Duval Medical Center, Jacksonville, Fla., on May 14, 1957, with a four-month history of a hacking nonproductive cough, fatigue, anorexia, and weight loss of 10 to 12 lb. For one month before entry, she had noted progressive exertional dyspnea and eventually had difficulty performing household chores. There were no known allergies or exposure to harmful dusts. Sputum studies for tubercle bacilli and a tuberculin skin test performed before admission were normal. A 70 mm. chest roentgenogram taken one year prior to hospitalization had been interpreted as negative.

On physical examination, the patient was sallow and became dyspneic from the exertion of the examination. Breath sounds were generally diminished, and a few fine inspiratory rales were noted throughout both lungs.

Radiographic studies of the chest disclosed extensive, mottled, and reticulonodular densities throughout all portions of both lungs. Interspersed between the nodules were small, radiolucent, cyst-like areas. There was no evidence of pleural effusion or hilar or mediastinal adenopathy. The heart appeared normal. The bony thoracic structures appeared intact. A bronchogram showed no evidence of bronchiectasis. A hemogram, intermediate-strength tuberculin skin test, sputum studies for acid-fast bacilli, fasting blood sugar, urinalysis, an L. E. preparation of peripheral blood, and x-ray views of the skull were negative. Serum cholesterol was 317 mg. %.

Because of inability to establish a diagnosis, we resorted to an open lung biopsy through a left thoracotomy on May 22, 1957. Scattered throughout the lung parenchyma there were nodules up to 3 mm. in diameter. Hilar nodes were soft and 2-3 cm. in diameter. A wedge of tissue was taken

from the lower lobe in the interlobar fissure. Microscopic findings were consistent with eosinophilic granuloma (see below). Recovery from the procedure was relatively uneventful.

On May 23, 1957, cortisone therapy was instituted with an initial dose of 300 mg. per day. This was decreased to 75 mg. per day over a period of one week. Dyspnea and cough improved considerably, and the patient was discharged on June 3, 1957. During the ensuing month, she became completely asymptomatic from a respiratory standpoint. There was moderate radiographic clearing of the pulmonary lesions, although diffuse linear and reticular shadows remained. The patient voluntarily discontinued cortisone several months prior to her last examination, on Aug. 16, 1958, but had remained well. Her timed vital capacity was 3,300 cc. (predicted normal, 3,100 cc.) with a three-second volume of 3,250 cc. (98% of total observed volume).

CASE 2.—A 57-year-old white farmer was first seen in the outpatient clinic of St. Vincent's Hospital, Jacksonville, Fla., on Jan. 26, 1957, with a two-year history of progressive exertional dyspnea, cough, fatigue, palpitations, and slight weight loss. He had not noted chills, fever, or hemoptysis. Cigarette consumption was one pack daily. There was a past history of asthma in childhood.

Physical examination revealed an alert, thin white man who appeared moderately dyspneic at rest. Respiratory rate was 32; blood pressure, 136/88; pulse, 82. Examination of the chest showed dorsal kyphosis, diminished expansion, generalized hyperresonance, and scattered crepitant rales. There were no heart murmurs or peripheral lymphadenopathy. Complete blood cell count was normal except for 4% eosinophilia. Urinalysis showed a rare white cell per high-power field but nothing else of note. Fasting blood sugar, blood urea nitrogen, and serologic test for syphilis were normal. Roentgenograms of the chest revealed an extensive nodular and reticular infiltration throughout all portions of both lungs. Interspersed between the reticular densities were numerous small lucencies, producing a honeycomb effect. The pulmonary artery segment was prominent and the diaphragm depressed bilaterally. There was no single large mass, pleural reaction, adenopathy, or cardiomegaly. Views of the hands showed minimal osteoarthritic changes.

The patient was then hospitalized for a short period for further study. Bronchoscopy was within normal limits. A biopsied right scalene lymph node showed no unusual features. Sputum studies for acid-fast bacilli and malignant cells were normal. Skin tests with tuberculin, histoplasmin, coccidioidin, and blastomycin antigens were negative.

Subsequently, the patient was followed at intervals in the clinic. It was observed that his dyspnea gradually increased. He was hospitalized again, on June 10, 1957, for further study and therapy. At that time, he was bedfast because of dyspnea and required intermittent oxygen. On June 26, 1957, a diagnostic right thoracotomy was performed. There were numerous adhesions between the parietal and visceral pleura. The lung showed less anthracosis than usual. Numerous small, round, firm, pink-gray nodular lesions were dispersed throughout the lung, and there were multiple small cysts up to 3 mm. in diameter. A biopsy specimen was taken from the right middle lobe. Microscopic findings were consistent with eosinophilic granuloma (see below).

On June 28, 1957, treatment with cortisone was started in an initial dosage of 300 mg. daily. Other therapy included salt restriction, mercurial diuretics, bronchodilators, and antibiotics. On this program there was marked clinical improvement. This was associated with mild to moderate roentgenographic clearing. By July 10, the patient was able to sit in a chair for short periods several times a day. By July 13, he was taking short walks in the halls and on July 18, he was discharged fully ambulatory from the hospital. Subsequent to that, he was seen in the clinic and had few respiratory complaints, although he was never able to perform more than mild to moderate physical activity. He discontinued cortisone of his own accord in the latter part of 1957 and was lost to follow-up after his last clinic visit, on April 1, 1958.

Microscopic Findings

Preparations of biopsied lung of both cases were stained with hematoxylin and eosin, as well as for elastin, collagen, and reticulin and by the periodic acid-Schiff method.[12]

In the hematoxylin-and-eosin-stained sections, the lungs of both cases were characterized by a diffuse, nodular or granulomatous infiltration dispersed throughout the pulmonary interstitium, involving septa, vasculature, and air passages in a random fashion (Fig. 1). Individual foci or nodules were composed of aggregates of histiocytes and eosinophils, occasional lymphocytes, and polymorphonuclear leukocytes with a fibrous tissue reaction (Fig. 2). The eosinophils were present as scattered individual cells and in nests or clumps. Although the predominant reaction consisted of a nodular interstitial thickening, adjacent alveolar walls were frequently thickened by a similar hyperplastic process (Fig. 1). Larger nodules appeared for the most part to be the product of a coalescence of smaller foci. Many small muscular arteries were thickened, chiefly as a result of intimal proliferation (Fig. 3); this finding was most marked in Case 2. In addition, the walls of individual vessels of all sizes were invaded, ulcer-

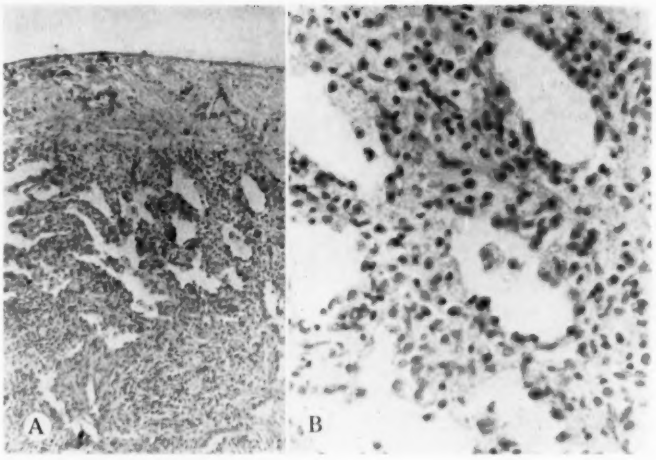


Fig. 1 (Case 1).—*A*, photomicrograph showing subpleural nodular granuloma with thickening of adjacent alveolar walls. Hematoxylin and eosin; reduced 30% from mag. ×64. *B*, higher magnification taken from same area as *A*, showing granulomatous thickening of alveolar walls. Hematoxylin and eosin; reduced 30% from mag. ×240.

ated, or obliterated (Fig. 6). Microcysts were noted in relation to scars and granulomata and appeared to represent both dilated bronchioles and alveoli. Many of these small cysts, as well as residual alveoli, were lined with cuboidal cellular linings (Fig. 7).

Both cases showed a fibrous tissue response which varied qualitatively and quantitatively. These changes were most clearly demonstrated with the reticulin stain. The more cellular granulomata, which predominated in Case 1, were associated almost exclusively with a proliferation of fibroblasts and reticulin (Fig. 5). This reticulin fibrosis and the reticulin stroma of normal alveolar structures seemed to give way or blend imperceptibly with denser less cellular areas of collagenous hyperplasia. Individual reticulin fibers were directly contiguous with lighter-staining collagen bundles.

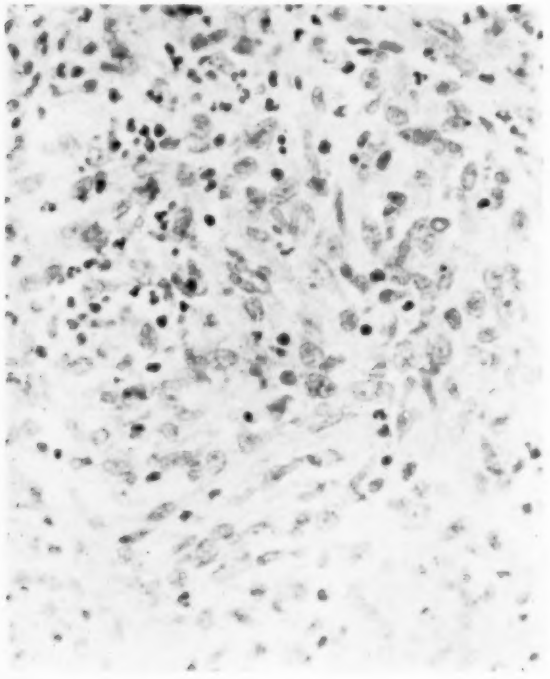


Fig. 2 (Case 1).—Photomicrograph showing detail of granulomatous reaction. Predominant cellular make-up consists of histiocytes and eosinophilic granulocytes. Hematoxylin and eosin; ×240.

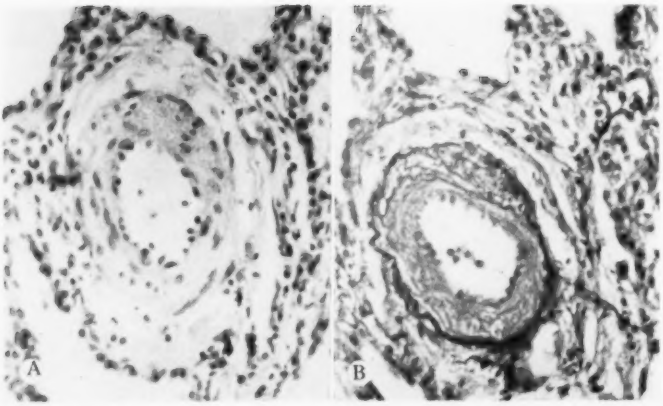


Fig. 3 (Case 2).—*A*, photomicrograph illustrating marked intimal proliferation. *B*, same arteriole as shown in *A*, stained for elastin. Note splitting and disruption of elastic lamina. Reduced 40% from mag. × 240.

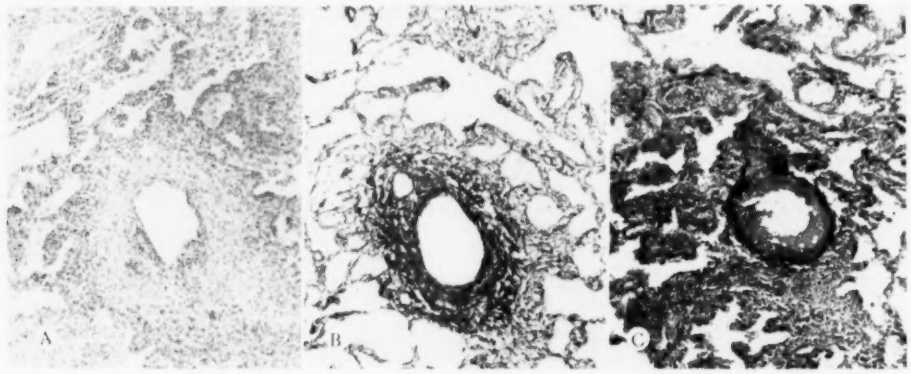
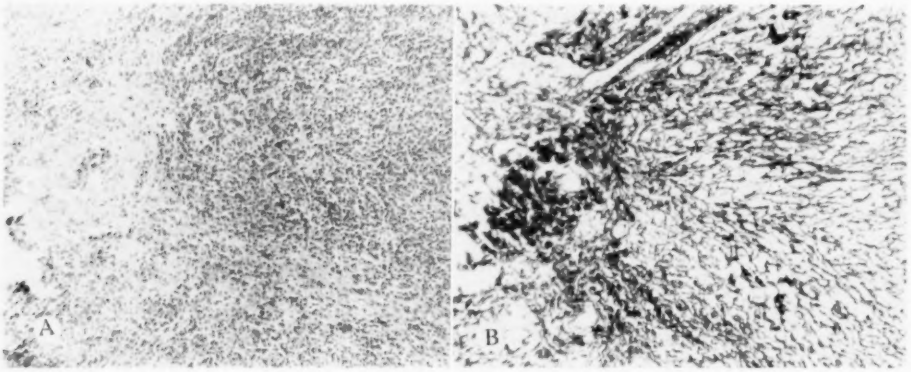


Fig. 4 (Case 1).—*A*, photomicrograph of an arteriole. There is marked invasion and thickening by the granulomatous process. Hematoxylin and eosin. *B*, same arteriole as shown in *A*, stained for reticulin. Inner portion of arteriole shows denser, more regular collagen bundles. These blend imperceptibly with finer, more irregular reticulin fibers in outer portion of vessel and alveolar walls. *C*, same vessel as shown in *A* and *B*, stained for elastin. Elastic lamina partially destroyed by granulomatous reaction. Reduced 45% from mag. × 64.

Fig. 5 (Case 2).—*A*, photomicrograph showing mixed granulomatous and fibrous reaction. Arteriole on left has been incorporated and almost obliterated by scar. Progressing from left to right, fibrous tissue becomes less conspicuous and is gradually replaced by cellular reaction. Hematoxylin and eosin. *B*, same section as seen in *A*, stained for reticulin. Denser, wavy collagen bundles merge gradually with finer, branching reticulin fibers on right. Reduced 35% from mag. × 64.



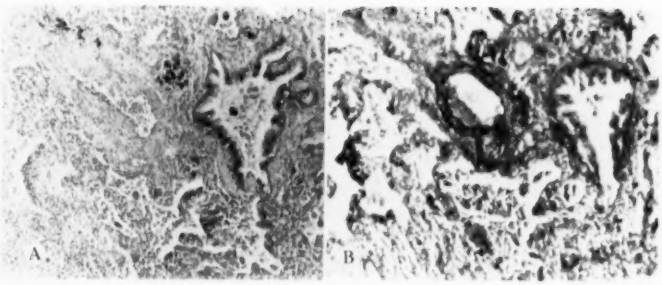


Fig. 6 (Case 1).—*A*, photomicrograph showing arteriole on left characterized by granulomatous invasion and intimal thickening. Bronchiole on right similarly invaded and ulcerated along its lower aspect. Hematoxylin and eosin. *B*, section stained for elastin. Elastic laminae of arteriole and bronchiole have both partially disappeared. Reduced 45% from mag. × 64.

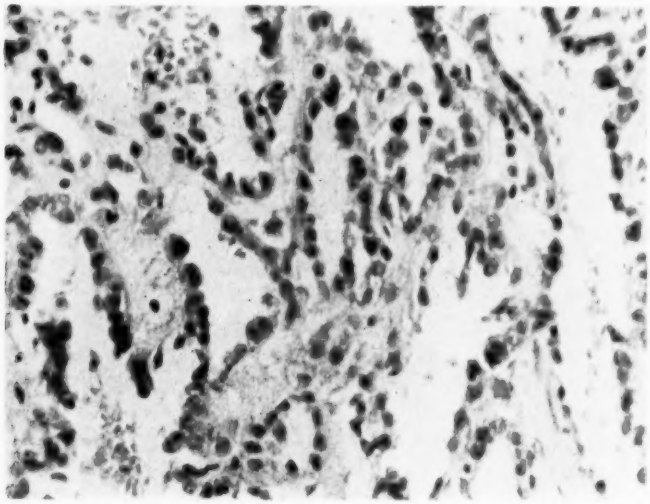


Fig. 7 (Case 1).—Photomicrograph showing fibrous thickening of alveolar walls and well-formed cuboidal cellular linings of alveoli. Hematoxylin and eosin; × 240.

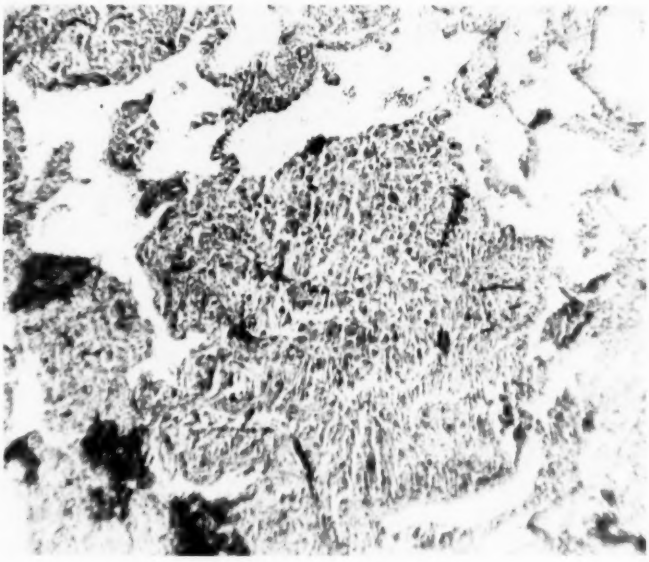


Fig. 8 (Case 1).—Photomicrograph stained for elastin. Elastic tissue is markedly reduced. A few isolated residual strands can be seen in a granulomatous nodule; × 64.

Collagen formation was more apparent in the second case, with symptoms of long duration. The association of reticulin with the more cellular, clinically acute disease of Case 1, the predominance of collagen in less "active" foci, and the blending between the two types of fibers in the individual cases left the impression of an orderly sequence of aging in these examples of pulmonary fibrosis. An initial reticulin increase was followed by an apparent collagen transformation and finally hyalinization.

With the elastic stain, a comparison of relatively uninvolved tissues with areas of greater disease disclosed that the elastic fibrils and laminae of alveolar walls, bronchioles (Fig. 6), and vasculature (Figs. 3, 4, and 6) became progressively more disrupted and scanty and finally completely disappeared, with increasing granuloma formation and scarring. Thus, in slightly thickened septa with minimal disease, the individual strands appeared merely separated. In the more nodular, frankly granulomatous areas, they were broken, frayed, and less conspicuous or absent. Residual elastica sometimes appeared as isolated black tangles or knots with no tendency to preserve previous alveolar outlines (Fig. 8).

Study of the sections stained with the periodic acid-Schiff routine did not yield findings of additional significance.

Comment

Thompson, Buechner, and Fishman [9] discuss the probability that different estimates of prognosis of eosinophilic granuloma, which have ranged from benign to grave, have been influenced by the unavoidable inclusion of some of the severer variants of the basic disorder, i. e., Hand-Schüller-Christian syndrome and Letterer-Siwe disease. The prognosis for pure eosinophilic granuloma usually has been considered bright. Auld,[8] for example, in his review emphasizes the mild course and good prognosis of patients with pulmonary eosinophilic granuloma. Such a concept, however, probably deserves some qualification. Autopsy demonstration that some fatal cases of honeycomb lung are due to eosinophilic granuloma [10] suggests that the outlook may be guarded. The critical status of our two patients is noteworthy in this connection. Both, presumably examples of pure pulmonary eosinophilic granuloma, were near the limits of their respiratory reserve. The first was reduced to a bed-and-chair existence, and the other was completely confined to bed, requiring intermittent oxygen.

Cortisone appeared to be life-saving in both patients. The younger patient, with relatively acute disease, is now clinically well; and the older person, although limited to a sedentary routine, was out of the hospital and enjoying a life of retirement when last seen. Both showed moderate radiographic clearing.

Different degrees of respiratory insufficiency and response to therapy in our patients may be related to different degrees of apparent conversion of reticulin to collagen. Since reticulin comprises the major part of normal alveolar support, reticulin fibrosis would seemingly constitute less obstruction to alveolar capillary gas exchange than collagen in pathological circumstances. It also seems reasonable that improvement would require less adjustment on the part of the organism. In the first case, the shorter, less severe illness; the widespread reticulin increase with a dearth of collagen, and the more satisfactory response to steroids, in comparison to Case 2, support this concept.

Elastic tissue destruction, which was so striking in our patients, has been observed in certain other types of pulmonary fibrosis. These include sarcoidosis [13] and atypical pneumonia of viral origin.[14] In contrast, it is not seen in other conditions, such as the Hamman-Rich syndrome [14] and long-standing pulmonary congestion.[15] These variations are consistent with pathogenetic differences. Eosinophilic granuloma, sarcoidosis, and atypical pneumonia seem to reflect a process of tissue destruction and/or replacement. Hamman-Rich syndrome and long-standing pulmonary congestion appear to be essentially a mixing of new fibrous overgrowth with preexisting tissues.

Nothing in our study or the work of others has clarified the basic cause of eosinophilic granuloma. Hence, any discussion of etiology falls within the realm of speculation. In view of certain features, however,

it is tempting to suspect an allergic origin. This viewpoint has been discussed in detail in Auld's paper.[8] Tissue eosinophilia and vascular changes, which are an integral part of the histology of eosinophilic granuloma, are frequently associated with diseases of known allergic etiology. Moreover, the histologic similarity to Loeffler's syndrome, periarteritis nodosa, and Wegener's granuloma, diseases of suspected allergic etiology, seems pertinent in this connection.

Summary

Eosinophilic granuloma is a systemic histiocytosis which is probably related to the Hand-Schüller-Christian syndrome and Letterer-Siwe disease. It may involve one or more systems of the body, including the lungs. Histologically, it is characterized by a proliferation of histiocytes and eosinophils with a fibrous tissue reaction. The etiology is unknown, but certain features are consistent with an allergic origin. Previous descriptions of pulmonary eosinophilic granuloma have emphasized its mild symptomatology, its good prognosis, and the frequency of diffuse interstitial infiltrations with associated polycystic changes in the lungs.

The two cases which constitute the basis for the present study were proven by lung biopsy. They showed some variation from previous descriptions and interesting connective tissue alterations. Both were severely disabled with respiratory insufficiency and appeared terminal. Cortisone therapy produced striking symptomatic relief in both instances. Microscopically "early," more productive lesions were associated with reticulin fibrosis. With progression of the sclerosing process, there was an apparent conversion of reticulin to collagen. Disruption and destruction of the elastica were pronounced and widespread in both cases.

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Myocardial Infarction as the Initial Manifestation of Polycythemia Vera

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Vascular occlusions occur rather frequently in polycythemia vera. While venous thromboses are said to be commoner, arterial occlusion or insufficiency has been reported to occur in approximately 18% to 30% of several series.[1-4] While at least one earlier report concluded that cardiac disease was uncommon in polycythemia vera,[5] later articles have shown coronary artery disease to occur clinically in from 6% to 10% of cases[1,4,6] and to be the cause of death in approximately one-fourth of a small series prior to the use of radioactive phosphorus in therapy.[3]

Myocardial infarction occurring early in the course of polycythemia vera is apparently rare; we have been able to discover but one brief reference to the occurrence of this complication, in a previously undiagnosed (and presumably asymptomatic) case.[7] The purpose of this communication is to report a 41-year-old patient who was discovered to have asymptomatic polycythemia vera at the time he had a myocardial infarction.

Report of Case

A 41-year-old automobile salesman was admitted to St. Mary's Hospital on Feb. 14, 1954, because of pain in the left chest and arm for the previous eight hours. His general health had always been excellent until approximately two weeks prior to admission, when he noted the onset of occasional pain radiating down the medial aspect of the left arm to the left elbow, usually on exertion. Eight hours prior to admission and shortly after awakening he noted a severer pain in the same location, followed shortly thereafter by a severe, constrictive pain in the left parasternal area. Approximately four hours later this pain was associated with nausea, vomiting, and moderate shortness of breath. Morphine sulfate, ¼ grain (16.3 mg.), was administered by a physician prior to hospitalization, with some relief of symptoms.

The patient's past history was completely normal except for the occurrence of a ureteral calculus at age 26 years (chemical analysis unknown). His father had died of "heart trouble" at age 84 years.

While he denied any previous cardiovascular, ocular, neurological, or gastrointestinal symptoms, he did, in retrospect, admit to a somewhat "ruddy" complexion for the previous six months.

Physical examination revealed a well-developed, slightly obese man who appeared anxious and was rather restless and who complained of pain in the medial aspect of the left arm. Blood pressure was 128/88 mm. Hg; pulse was 112 per minute; respirations were 20 per minute, and temperature was 98.6 F. There were no abnormal physical findings; splenomegaly and lymphadenopathy were not noted to be present.

Urinalysis revealed specific gravity of 1.032, a trace of albumin, 0.75% sugar, and a small quantity of acetone. Subsequent urinalyses have been negative for albumin, sugar, and acetone. A fasting blood sugar determination later was 105 mg. %. The hemogram revealed a red blood cell count of 6,500,000, hemoglobin of 21.8 gm. %, and a hematocrit of 64%; the white blood cell count was 24,950, with a slight shift to the left. Platelet count several days after admission was 270,000. Serological test for syphilis was negative. Total serum cholesterol was 230 mg. %.

The electrocardiogram revealed a sinus tachycardia with ventricular premature contractions and changes which were interpreted as suggestive of early anterolateral myocardial infarction. Serial electrocardiograms demonstrated the evolution of an anterolateral myocardial infarction (Figure). A chest roentgenogram was within normal limits.

Treatment consisted of bed rest, analgesics, sedatives, and coronary vasodilator drugs. Anticoagulation with bihydroxycoumarin (Dicumarol) was instituted, and the prothrombin time was maintained at 20%-30% of normal during the next four weeks. On the fourth day after admission the first of five venesections of quantities ranging from 300 to 400 cc. of whole blood was

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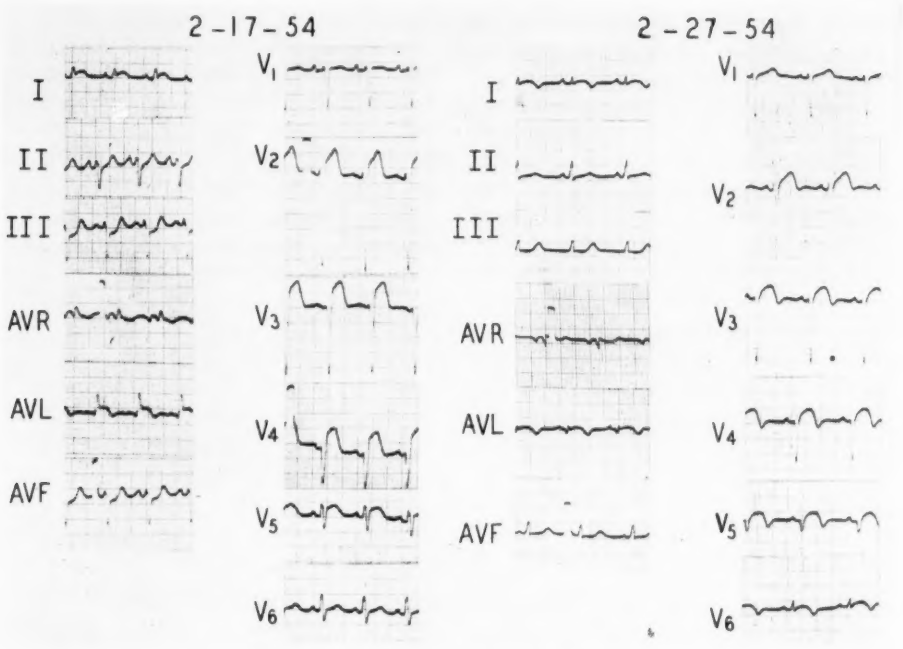

Electrocardiograms taken one week apart.

performed. After the removal of approximately 1,800 cc. over a six-day period the hemogram revealed a red blood cell count of 5,500,000, hemoglobin of 15 gm. %, hematocrit of 46%, and white blood cell count of 13,600. On March 10, 1954, he received 2.25 mc. of radioactive phosphorus intravenously.

The patient experienced no pain after the third day in the hospital, and his course was uncomplicated. There were no adverse reactions to the venesections. He was discharged on March 13, 1954, for further convalescence at home.

Subsequently he remained well until June, 1956, when he developed thrombophlebitis of the right long saphenous vein and was again hospitalized. At this time the spleen was palpable 2 to 4 cm. below the left costal margin. A hemogram revealed a hemoglobin of 16.9 gm. % and a hematocrit of 54%; white blood cell count was 7,350. In addition to the usual measures, phlebotomies were performed until the hemogram was normal, and on June 19, 1956, he received 3.1 mc. of radioactive phosphorus intravenously.

After this he remained asymptomatic and had normal hemograms until December, 1957, when it was noted that his hematocrit was again slowly rising. On Jan. 26, 1958, his hematocrit was 50%. After a 500 cc. phlebotomy he received 4.0 mc. of radioactive phosphorus intravenously. Subsequently, frequent hematocrits have been normal.

At no time since his original hospitalization has this patient had signs or symptoms of coronary artery disease or of congestive heart failure.

Comment

In addition to the earlier report by Brown and Griffin, in which they conclude, "Cardiac enlargement and cardiac disease were noticeably absent,"[5] other authors have been unimpressed by the incidence of coronary artery disease in polycythemia vera. Wiseman and his associates commented that it was surprising that deaths from arterial thromboses in treated cases of polycythemia do not differ significantly from those in the general population in this age range "in view of the greatly increased incidence of thrombosis (other than cardiac)" in cases treated without radiation.[8] In his textbook of hematology, Wintrobe states: "Cardiac symptoms are not particularly prominent and cardiac hypertrophy is more frequently absent than present. Vascular disease, on the other hand, is extremely common. . . ."[9]

While a number of authors noted an association between polycythemia vera and coronary artery disease, there were only occasional case reports in the earlier literature.[10-12] In 1937, Norman and Allen stated that coronary thrombosis does not appear to occur with as great frequency as does thrombosis in other areas in polycythemia vera; however, in their series there were almost equal numbers with coronary artery disease and with either cerebral or peripheral artery disease.[1] In reporting three autopsied cases in which coronary occlusions were found, Miller stated that, while coronary artery thrombosis is not frequent in polycythemia, "It is not as rare as is generally believed."[13]

Tinney and his associates arrived at similar conclusions; in a series of 163 patients with polycythemia vera they found an incidence of 6% for clinical coronary artery disease. They stated, "Coronary arteries are not involved so often as the cerebral or peripheral vessels, but the incidence of coronary occlusion in polycythemia is higher than it is in the general population."[6]

Reviewing 32 polycythemia vera patients treated with measures other than radioactive phosphorus, Stroebel, Hall, and Pease found coronary thrombosis to be the leading cause of death (25%). In the same report they noted that, of 22 patients treated with radioactive phosphorus, coronary occlusion was the cause of death in only 2%.[3] Lawrence found coronary artery disease as the cause of death in 7% of 57 patients treated with radioactive phosphorus.[4] He noted clinically recognizable coronary thrombosis to occur in 4% of a total series of 201 patients.

All of the reported cases of myocardial infarction occurring in association with polycythemia vera have occurred in patients in whom the diagnosis of polycythemia had been established months or years previously. The only exception to this, prior to the present report, was in a 56-year-old woman briefly mentioned in the book by Wright, Marple, and Beck.[7] The only relevant information given in that report is that polycythemia vera was diagnosed during the patient's admission for myocardial infarction. She was treated with anticoagulants and venesection. Of 1,031 cases of myocardial infarction included in the above study, 4 had polycythemia vera.

James, Post, and Smith reported the case of a 41-year-old woman with hypertension and polycythemia vera who had a posterior myocardial infarction.[15] However, it is not clear from their report whether the diagnosis of polycythemia vera had been established prior to the infarction nor whether previous manifestations of the polycythemia had been present.

Friedberg states, in reference to concomitant coronary artery disease and polycythemia vera, that he believes the polycythemia is a contributory cause and not merely a coincidental factor in the coronary artery disease.[14]

While myocardial infarction is not uncommon in 41-year-old men in the United States, we believe that in the case reported here the polycythemia, even though of apparently recent development, was a contributory factor.

Summary

The occurrence of a myocardial infarction as the initial manifestation of polycythemia vera in a 41-year-old man is reported, and the relevant literature is briefly reviewed. This is apparently the first such case completely reported.

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Evolution of Modern Medicine

Osler's Unfinished Business

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This section, which has as its primary purpose a review of the contributions of medical investigators and observers of the past to the present-day concepts of disease, is under the special editorship of Dr. Arthur Bloomfield, 2398 Sacramento St., San Francisco 15.

His editorial in the August, 1957, issue of the A. M. A. Archives of Internal Medicine, *gives further detail of what it is hoped to accomplish in these articles. Contributions or comments for this section may be sent directly to Dr. Bloomfield, or to the Chief Editor for transmittal to him.*

Sir William Osler left an unforgotten legacy to medicine. He was an ideal physician. He turned the hospital into a teaching institution. He popularized ward teaching of medical students. He reemphasized standards of medical etiquette. He brought medical ethics to the highest plane. He wrote a textbook that opened the doors of medical research. In addition to these, he left suggestions of the greatest merit for the improvement of present-day and future medicine.

Osler, though a clinician, did his own postmortem examinations. Edward Janeway and Austin Flint, clinicians of outstanding ability, did their own postmortems too. There is no question that the average doctor with a little special training in postmortem technique and with the assistance of a pathologist can also do his own postmortems. There is no reason why a doctor so trained cannot assist more frequently at postmortems in the hospital; nor is there any reason why he cannot do them at the home or the funeral parlor. The knowledge he obtains from this added responsibility will be of inestimable value to him and to his patients.

The second suggestion relates to the mastery of foreign languages. The cosmopolitan character of medicine makes the knowledge of foreign languages paramount. Writes Osler, "If the work of a scholar is to be effective he must keep in touch with scholars in all other countries. . .and it is not only book knowledge and journal knowledge but a knowledge of men that is needed." Doctors must be encouraged to take an active part in foreign medical meetings and be at home with foreign ways of thinking. It is easy to see how the medical curriculum of the future will incorporate linguistic studies with medical teaching. With such a preparation the student is able to take his *Wanderjahr,* a period of six months to a year devoted to study in foreign clinics. One can foresee the day when fourth-year medical students will study at foreign institutions. Osler also encourages graduate doctors to undertake "quinquennial brain-dusting," by which they study at another institution for three to six months every five years of their practicing life. Such a movement, carried on both here and abroad, would go far toward providing a universal view and a supple mind. Some specific program for international coordination of medical education for undergraduates and graduates is sure to become a part of the medical scene. That Americans are actually taking advantage of training abroad is apparent from the reports of the Institute of International Relations and the American Medical Association. About 2,000 medical students are studying in France, Germany, Italy, Switzerland, Holland, Belgium, Spain, Scotland, Ireland, Czechoslovakia, Mexico, Greece, England, and the Scandinavian

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countries. There are, according to Dr. Morris Fishbein, about 1,000 American doctors and 100 faculty members taking postgraduate instruction abroad. These figures will undoubtedly swell many fold as doctors appreciate the advantages of foreign study.

Osler said, "The work of an institution in which there is no teaching is rarely first class." This idea leads to the suggestion that medical schools work hand in hand with small hospitals in their communities. Medical societies have done splendid service in raising hospital standards, and these, operating together with medical schools on an administrative level, can make substantial progress in providing high-grade service to the public. The idea of an international clearing house for teachers has special merit. Under such a plan experts can be called upon readily to give their knowledge to medical schools and medical societies deficient in a specialized type of teaching.

Osler complains that state examining boards insist on a minimal amount of professional knowledge, with no regard to the state of the doctor's knowledge 5 or 10 or 15 years hence. It is easy to see how a physician can have added no more knowledge during all his practicing years than what he learned in medical school. Does the state have a right to determine whether a physician is capable of serving the public, and this at any time during his practicing life? Why should a state-supervised examination be the agency to coerce the doctor to be abreast of his field? Why cannot the doctor so school himself as to let his life be a continuing process of postgraduate education? Osler felt that the demands of the individual licensing boards of each of the states of the United States and of each of the provinces of Canada are no less than an affront to the doctor who has undergone a satisfactory training at an approved medical school and at an approved internship. Clearly, the subject of medical licensure and professional capability needs reevaluation on a state, national, and international level.

"The incessant concentration of thought upon one subject, however interesting, tethers a man's mind in a narrow field," Osler notes. Osler developed the habit of reading classical literature before he retired. There is no better way of keeping the mind warm, sympathetic, cheerful, understanding, and charitable. In view of the importance of the study of the humanities, some institutions like Johns Hopkins and McGill are actually introducing the study of literature, art, music, religion, philosophy, and sociology as part of the daily activity of the medical student. Not only should such studies be taken in the student years but they should continue on through internship, residency, and practice and be incorporated into the very program of the scientific meeting.

Osler's great strength lay in his solid knowledge of the history of our profession. "In the continual remembrance of a glorious past individuals and nations find their noblest inspirations," he says. "We must maintain a sense of continuity with the past, as the ancient physicians did in their festivals and their ceremonies commemorative of the dead. Less and less attention is being given today to the past and we are missing that energetic glow that emerges from the bye-gone. We must cherish the memories of the old as an inspiration to the new." The doctor who is concerned with character building, the research man who is seeking refreshing ideas, the teacher who is anxious to know the trials of scholars of another age will find rich treasures awaiting him by the study of the past. Hippocrates and Laennec and Frerichs then become living persons, each of whom has a message to deliver. The teaching of medical history thus becomes an integral, not an accessory, part of the medical curriculum and should properly take its place beside the teaching of such subjects as physical diagnosis or pharmacology. The inclusion of historical discussions in medical journals and medical meetings provides the breath, solidity, and humility that we so much need today.

As long ago as 1902, Osler encouraged the preservation of local medical archives—letters, manuscripts, pictures. Such memorabilia have a magnanimous influence upon the character of medicine. They are indeed a thread that binds us to a previous era. No one will question the importance of a national archives of medicine. But the most practical solution lies in the development of an archives section in each local medical society.

His suggestion of a museum of charlatanry has great merit. There is a necessity in our country for a center that has as its fundamental purpose the collection, exhibition, and lending of materials and literature relating to fads, quackery, superstition, fraud, and tartufism. Such an institution will bring into strong light the pitfalls and warning signs of medicine, such as cancer cures and indiscriminate bloodletting. The effect on our profession and the public can only be most wholesome.

Thus Sir William Osler leaves us with twelve ideas that can be developed for improvement of medicine. In review, postmortems done by the clinician himself, mastery of foreign languages, the *Wanderjahr* for the medical student, quinquennial brain dusting for the doctor, international coordination of undergraduate and postgraduate medicine, international clearing house for teachers, international cooperation on medical licensure, cooperation of medical schools with the small community hospital, reevaluation of state examining boards and their functions, teaching of medical history to students and doctors, teaching of the humanities in medical schools and medical meetings, and the creation of medical archives and museum of charlatanry. All of these are acorns that can grow into mighty oaks; indeed, some of them have already begun to sprout.

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Reviews of Internal Medicine

Neuropsychiatry

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The year 1958 brought to us whose main interest is the brain two grievous losses. J. Godwin Greenfield, the great neuropathologist, of Queen Square, London, died in Washington, D. C., and Karl S. Lashley, the distinguished Harvard psychologist, died in France. Greenfield was the dean of neuropathologists, in the international sense, and was for years the Dean, in fact, of the School of Neurology at the National Hospital, Queen Square. Here a generation of rising neurologists has looked up to him as a great teacher and a lovable, kindly man. As pathologist of the hospital for over 30 years he accumulated a vast experience. He was not only a pathologist but a good clinical neurologist who understood diseases of the nervous system in their broad, biological setting—physiological, genetic, and clinical, as well as histological. He died while working at the National Institute for Neurological Diseases and Blindness, at Bethesda, Md., where he had more than once been welcomed as colleague and consultant.

In 1921, he published, with Buzzard, his "Pathology of the Nervous System," a modest book but the first of its kind and a great boon to students. When he died, in January, 1958, he had just finished reading the page proof of his monumental volume, "Neuropathology," [1] which appeared in April, 1958. It is a book of 640 pages, written in collaboration with his younger colleagues, Blackwood, McMenemy, Meyer, and Norman. The chapters on general pathology of the nerve cell, infectious diseases of the central nervous system, traumatic lesions, demyelinating diseases, system degenerations, neuritis, and cranial malformation are by Greenfield himself. Especially helpful in a difficult field is his classification and description of the encephalitides, both infectious and "post" or "para" infectious. The complex relationship of these diseases to the "demyelinating" group is discussed in an illuminating way. He considers the allergic reactions as important but thinks multiple sclerosis is probably due to microbic or viral invasion. There is a fine chapter, by Blackwood, on vascular disease; Meyer writes on epilepsy, anoxias, intoxicants, and metabolic disorders; McMenemy, on dementias, and Norman, on malformations of the brain and birth injury. Each chapter gives an interesting historical background. The bibliographies are extensive. The book is beautifully printed and illustrated. It will uphold Greenfield's fame for many years to come and be useful to internists as well as specialists.

Karl Lashley has been conspicuous for 40 years not only in his official field of psychology but also in neurophysiology and experimental neurology. His experimental work was clean-cut and telling; his thinking was incisive, courageous, and witty. He was the psychologist oftenest called upon by neurologists and psychiatrists to speak at their meetings and join their symposia. It was a delight to hear his clever and wise discussions after the boredom of a series of ponderous papers. His own contributions concerned the fundamental questions that a lesser man would have hesitated to tackle.

He wrote a series of 12 "Studies of Cerebral Function in Learning" between

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1917 and 1943, which established him as a leader in the experimental field. Other important papers (to choose only a few) for the neurologist and psychiatrist were "Integrative Functions of the Cerebral Cortex" (1933), "Experimental Analysis of Instinctive Behavior" (1938), "The Thalamus and Emotion" (1938), and "In Search of the Engram" (1950).[2] Fortunately, these papers and about 25 others, with a biographical introduction, are to be published in a memorial volume in the near future.[3]

If one wishes to read an amusing and instructive example of polemic writing between two able exponents of opposite ways of thinking, one should read the exchange of letters between Lashley and Colby,[4] a psychoanalyst. To my mind, nobody wins, or rather both win, because both are keen, polite, and as tolerant as possible; they differ in method and training; neither one lays claim to exclusive truth.

Memory

Lashley spent much of his life in search of the "engram," investigating the neural basis of learning. Obviously there can be no learning without memory, and so the investigation of memory is a fundamental research for all the psychological sciences. The older generation of scientists was brought up on Pavlov and taught to think of learning in terms of conditioned reflexes. Pavlov's experimental observations have lost none of their significance, but his theoretical explanations will not survive in the light of modern neurophysiology. His theories rested on conceptions of fixed-reflex arcs and localized cortical centers functioning by means of excitation, inhibition, and irradiation. Thorpe[5] says (page 135), "The work of Lashley on the effects of cortical ablation on the retention of the maze habits in rats seems to have disposed finally of any assumptions which would involve localized memory traces—and electro-encephalogram studies appear to have reinforced this conclusion."

"Learning and Instinct in Animals," by W. H. Thorpe, is a most useful book, beautifully written, scholarly, and well documented. The author is a zoologist, comparative psychologist, and ethologist. He teaches at Cambridge University. No one interested in memory can afford to miss reading this book. It is of interest to psychiatrists because it takes up such topics as "drive," "instinct," and "learning." Chapter II is a remarkable summary of "The Nature of Drive and Its Place in the Theory of Instinct." The next chapters are on habituation, trial and error learning, conditioning, and insight learning. In short, they make up five short expositions on learning theory which are a boon to those who have not read extensively in modern psychological literature.

The ethologists in looking for drives to explain behavior have used present-day knowledge of endocrine organs and libido and have added a neuronal mechanism. From animal psychology they have concluded that perception is an important source of drive. Thorpe says:

> . . . perception itself is essentially a learning process—for obviously the perception of relations must involve comparison and comparison in its turn involves memory and expectation, and so is clearly a form of learning. So it was suggested that perception is itself one of the fundamental motivating entities of animals, and as such could provide one of the bases of the internal drive. Perception and response were presumably originally inseparable in the primitive animal, and obviously response is still the only means that we have of testing animal perception. If, then, perception and response were originally inseparable, we can consider evolution as having been the process of extending and specializing both; perception by the development of sense organs, response by the elaboration of effective mechanisms, the two integrated by the central nervous system. And, as experiments demonstrating the principle of "re-afferentation" show,—a major step in the organization of animal behavior has been the development of methods whereby the individual or the species selectively ignores certain stimuli—and comes to attend to the relatively few that concern it. Thus, insofar as the original faculty of perception retains or increases plasticity during evolutionary development, it becomes the various learning processes that we know. Insofar as it becomes canalized and stereotyped in phylogeny, it becomes instinctive behavior.

The latter part of the book is a description of the learning ability of animals, examples being given from each of the main groups, from Protozoa through worms, mollusks, and reptiles to birds and mammals. It is fascinating reading.

Thorpe has critically reviewed an enormous amount of work on memory. He believes that even in protozoans like Paramecium it is a fairly safe conclusion that true learning has been demonstrated. In sea anemones the evidence is even more convincing. Starfish display true habituation and some associative learning. In worms and mollusks the ability to learn is easily proved. The extraordinary experiments of Young [6] and his associates demonstrate that the octopus can learn to distinguish various figures, a square from a long rectangle and from a diamond. The conditioning of the octopus' responses is not difficult, yet his brain consists of a few relatively simple ganglia, the largest of which are optic lobes. It was even shown, by operating on and removing some of the ganglia, that the optic lobe had a mechanism for immediate memory whereas the vertical lobe was able to prolong memories.

In insects, although the central nervous system is simple, memory and learning are demonstrated in many complicated behavioral patterns. Some wasps inherit marvelous rituals for breeding and feeding their young. Bees show marked ability to learn and communicate in addition to their intricate series of instinctive acts.

In vertebrates memory mechanisms are clearly of great importance. The brain has developed at the head end of the animal into an organ of great complexity. In fish, amphibians, reptiles, and birds the patterns of behavior are largely inherited, but some learning is added onto the instinctive background, and most acts are the result of instinct plus learning. This becomes more obvious as we ascend the phylogenetic scale, and so in mammals the learned behavior begins to dominate the instincts. This is conspicuous in man, where instinctive patterns are considerably masked by intelligence (defined as the more adaptive, learned part of behavior).

The study of memory in man is difficult because of its great complexity and because the phenomena appear at so many levels of integration from cord to cortex. Penfield, a surgeon with a unique experience in operating on epileptic patients, says [7]:

> A clinician must contribute to Science as best he can from very different material and as chance presents it. The brain and the mind of man constitute evidence that is denied to the experimental physiologist. Man talks and thinks for himself, and that constitutes our great opportunity. But the physiological clinician cannot control experiments nor plan them. Disease and stress and accidents perform experiments on the brains of men and women and children. We can only wait and watch and rationalize, as opportunity presents itself.

Ritchie Russell, President of the Neurological Section of the Royal Society of Medicine, chose memory as the subject of his presidential address in 1958 [8] and of his Morison lecture in Edinburgh.[9] He gave many interesting examples of disorder of memory from his wide clinical experience; he talked on neurophysiology, and pointed out psychological principles that could be applied to teaching children. Penfield, in his Sherrington lecture at the University of Liverpool,[7] also discussed memory and summarized his stimulation experiments on the cerebral cortex of conscious patients. Walshe [10] wrote a smart but destructive discussion of Penfield's theories, without the saving grace of any original contribution. So, within a year, three leaders in neurology have expressed themselves on this fundamental and controversial aspect of nervous function.

Penfield's lecture [7] has been published in a small book; it summarizes some of his great work on stimulation of the human cortex, in which one sees how he has approached each of his hundreds of craniotomies, done under local anesthesia, as if it were a physiological experiment as well as a therapeutic procedure. The book reviews two important contributions: First, his discovery that in certain epileptic patients

he could elicit by stimulation of temporal cortex "a shorter or longer sequence of past experience. The subject relives a period of the past although he is still aware of the present" (page 23). This Penfield calls an "experiential hallucination," because the patient really saw and heard vivid scenes from his past life. These were reported as he lay conscious on the operating table while stimulating electrodes were being applied to his brain. Here is something entirely new to physiology, and it came to the operator as a "complete surprise," although it "might have been predicted from the previous observations," especially those of Hughlings Jackson. Another form of psychical response elicited from this region is called an "interpretive illusion": The patient reports a sudden *mis*interpretation of his present experience. When the temporal cortex is stimulated, things suddenly seem strange or strangely familiar (the "déjà vu" of Hughlings Jackson); they may grow larger or smaller, nearer or more distant.

The second contribution is the observation that stimulation of an isolated gyrus in a sensory region of the cortex can cause sensations in the patient. Since the gyrus was surgically cut off from all lateral associations with other cortical areas, this indicated that impulses were returning to subcortical structures, and the observation was a starting point for Penfield's theory of a "centrencephalic system" in the diencephalon. The observation is of importance whether or not one agrees that this centrencephalic system is the great integrator. At least the corticofugal neurons are an important relay in the chain of integration that subserves many mental processes.

Such remarkably complete remembrances as Penfield elicited are a very different sort of phenomenon from simple memory (defined as the basic function of nervous tissue that provides for reaction in the light of past experience). Until this basic memory mechanism is discovered, one cannot hope to understand the scenes from the past evoked by stimulation of the human brain. The mechanism by which memories are stored is still a mystery. But recent work of Konorski, Hebb, Eccles, and Pringle gives one a basis for postulating a possible mechanism. All these and many other theories are critically discussed by Thorpe.[5]

To summarize this briefly is difficult, but one can begin by saying that the early theories that postulated a memory stored somehow in a nerve cell are impossible simply because there are not enough nerve cells to carry the memories of a lifetime. Moreover, Lashley disposed of these theories by his ablation experiments on rats which proved that there could be no local memory traces. Some more dynamic mechanism must be postulated. The cybernetic theory that memories may be stored as reverberating neuron circuits seems to be ruled out (at least for lasting memories) by the experiments which show that all electrical activity in an animal's brain may be stopped by lowering the body temperature; yet when the animal recovers, it can be shown that conditioned reflexes are retained.[11] Konorski[12] postulated that the coupling of two neurons by conduction of impulses might effect the growth of the knobs at the synaptic contacts, and if, as has been estimated, there can be 1,300 synaptic knobs on a single nerve cell, the enormity of the number of possible combinations of connections approaches what might be needed for memory storage. Hebb thought it possible that a structural change could work with a reverberating trace, and Eccles considers the essential mechanism to be the synaptic knobs in contact with a specialized membrane, both of which are structurally changed by passage of nerve impulses. There is, in fact, evidence that axons can change volume after repeated stimulation. This makes Lashley's theory of "interference patterns," like those of the waves of a fluid surface, more than a good guess. Pringle[13] suggested that a mechanism, analogous to the synchronization in coupled electronic oscillators, could be the model for

a learning process in the brain. Thorpe points out that any of these theories, or combinations of them, are at present highly provisional, but they are not preposterous and are based on the rapidly advancing research into the electrophysiology of the nervous system.

In short, at present there is reason to believe that the mechanism by which memory traces are stored in the central nervous system is an active conduction of nerve impulses through neuron circuits which relate one neuron to others in certain patterns. These are not strictly local but are repeated over more or less extensive areas of nerve tissue. The patterns may be perpetuated by morphological changes in the end-knobs of synapses and the subjacent membrane of the next neuron. The uniqueness is not in any one synapse but in the pattern of relationships of one neuron to others. Arousal of one or several of these patterns might evoke memories of varying degrees of complexity.

Tolstoy [14] wrote, in Anna Karenina, in 1875: "Is there a line to be drawn between psychological and physiological phenomena in man? If so, where?" Thorpe in his masterly review shows us where we may look for such a line in 1959, but no one nowadays expects to find any arbitrary line, only a difference in degree of complexity of the phenomena studied and in the point of view of the observer. There is a great temptation to talk about memory and learning in general as if we knew all the steps in the process from the physical chemistry of nerve conduction to the teaching of children in school. Some authors leap from physics to pedagogy. The fact is we know a few of the steps and make educated guesses at others. When talking in the area of discourse of polarized membranes, synapses, and nerve conduction, we should stick to that and not try prematurely to relate it to clinical material when even its relationship to well-controlled experiments on animals is not clear.

In the field of clinical neurology and neurosurgery there are many important problems concerning the loss, distortion, and evocation of memory. The recorded observations from Jackson to Penfield and Bingley [15] afford fascinating reading. A vast amount of work is still to be done on human subjects before order can be brought out of the data. Only a limited amount of understanding can be gained by comparing man and laboratory animals.

The clinical psychologists test such phenomena as memory, retention, attention, and preoccupation. The psychoanalyst works with repressions—blocked memories which are forgotten but not lost. The hypnotist can elicit memories that seemingly never reached consciousness at all. Here is another area of discourse with three libraries of literature.

Some great neurologists of the future may put all this together into one mosaic picture. But today each expert in his own field might more effectively work at making more blocks for the mosaic. At present we just do not know enough to argue from one area of discourse to another without being pretentious.

Perception

Perception plays a great part in determining the behavior of a person. The most obvious examples are persons in whom a complete loss of one "sense" deprives them of one type of contact with the environment; the deaf, the blind, the anosmic. These are peripheral disturbances, and actual reception of stimuli is blocked. Perception is a more complex phenomenon involving central processes; more integration is involved, and integration is the function of the central nervous system from cord to cortex. Central lesions may do the blocking in tracts or cells in cord, brain stem, thalamus, or cortex. The cases in which lesions cause perceptual difficulty are much less common than those with disorders of perception due to more complex factors, grouped under the term "psychological." This would include disturbances in intelligence, goal

orientation, drives (such as hunger and thirst), or personal needs. Perception, indeed, must be looked upon as a function modified at every level of nervous integration. Cruickshank, Bice, and Wallen [16] express it well in the introduction to their monograph, saying, "The study of perception may be defined as pursuit of the question why things 'look' as they do and why they do not 'look' the same to all persons." These authors give an excellent exposition of the way in which tests of perception may be applied to a practical problem: in this instance, the question of the relation of perception to the performance of children with cerebral palsy. Their study indicates that there is impaired perception in these children, especially for the figure-background relationship.

A symposium was held at Harvard, in June 1958,[17] on Sensory Deprivation, in which neurologists, psychologists, and psychiatrists from many parts of the United States, Canada, and Europe took part. It brought into timely focus the work on this subject begun * in Hebb's laboratory [18] in Montreal, in 1952. Normal persons submitting themselves to severe restrictions of sensory stimulation have been shown to develop hallucinations and delusions within a few hours. To be put in a dark, quiet chamber and floated in a warm bath to prevent tactile or thermal stimulation is a much severer ordeal than anyone had imagined. The study of sensation and experiments on perception are old and accepted parts of academic psychology. If the psychologists are less dogmatic now, it is probably because of the revolution in our understanding of the central nervous system that has taken place in the last 10 years. One no longer thinks in terms of stimulus and response through an integrating switchboard mechanism. New electronic methods [19] have made possible a new and more dynamic understanding of the physiology of the central nervous system. To the reflexology of Sherrington and Pavlov has been added new knowledge of reverberating circuits, feed-back systems, communication theory, and the central modulation of sensory perception. A new picture of the activity of the brain emerges, a picture of a prosencephalon alerted to receive selected stimulation by mechanisms in diencephalon and mesencephalon, which in turn can influence peripheral sensory input. Moreover, it is a picture of each of these levels acting on the others by signals from internuncial circuits. The whole concept gives an idea of the continuity and rhythm of cerebral processes. It explains the function of many neurons and short tracts that until recently had only anatomical names but no meaning.

In all this, perception plays a great part. But who can define perception? Can we simply call it a word for how things look to us and why they look differently to others? This is vague and unsatisfactory and suggests how much we need a critical study. When Hebb, Lilly, and their co-workers had the ingenious idea of studying perception in human beings by means of sensory deprivation and especially when they courageously acted on the idea and performed these experiments, they made a great step forward. It is only five years since they published their first paper on this subject, but one has only to look at the content of this symposium to see how quickly and fruitfully the work was taken up by others. A new method of attack on an old and controversial subject is not often so successful. The problem is old, fundamental, and much discussed because it has to do with reality. The sense of reality and reality-testing are central themes for psychiatrists, just as an understanding of the physiology of perception has been called the basis of psychology. Consciousness is another enigma that may be approached by the methods of sensory deprivation. The mechanism of attention deserves more attention than it receives from psychologists. Adrian's brilliant suggestion at the "Laurentian Symposium," in 1953,[20] that an editing or selecting function takes place in the

* By Bextion.

reticular formation may point the way to an understanding of how attention works. Certainly it helps one to understand how perception may be modified in the central nervous system.

These studies will enlighten our quest for knowledge in diverse fields. For example, the symptoms of the deprived child with "atypical" and "autistic" reactions may well be related to the phenomena seen in adults after experimental sensory deprivation. What such deprivations may do to the growing brain is still an all-important field for physiological and psychological exploration. Studies on the effects of sensory deprivation may provide us with data valuable to communication theory and cybernetics. They touch on the discussions about what is objective and what is subjective, popular now in existentialist philosophy. The sort of hallucination evoked by sensory deprivation in different persons has been studied; one gets some clue as to which perceptions have been stored and which are closest to consciousness. Here is perhaps a method of learning more about memory.

Neurosis, Philosophy, and Existentialism

Neurosis may be described as an emotional disorder largely caused by maladaptations in personal relations. As such it is by definition mostly a psychological problem. I say "largely" and "mostly" because I believe in multiple etiology. "Diseases" and "disorders" are rarely if ever the result of one cause; they are the reaction of a person to a particular evironment—to a sequence and concatenation of events (genetic, physiological, and social) at a certain time in his life history.

Neurosis is, therefore, bound up with personality development from the cradle to the grave. It presents medical, philosophical, and moral problems. Medically it is concerned with the treatment of the many persons who consult physicians for relief of psychogenic symptoms. As a human phenomenon neurosis touches fundamental philosophical problems. What am I? What am I here for? What are the aims, goals, and satisfactions of life? Have I choice, "free will," or only automatic reactions? From the moral point of view (to mention only one question), one might ask: Why do I make good or bad choices?

Many physicians believe that these problems have nothing to do with medicine, that attempting to modify the personality of the patient is not the physician's job, that he has been trained in other techniques and would leave this to the minister or counselor. This is an understandable but benighted point of view, because poor adaptation in personal relations ("neurosis") is now known to play an important role in symptom formation in many medical and surgical disorders.[21] Moreover, studies in communication and in the doctor-patient relationship show that the doctor does affect the patient's personality, for better or worse, whether or not he means to do so.[22] There is also the enormous problem of how to treat those who suffer from anxiety. At the present time there is an almost universal *Weltschmerz* among literate people, fostered by conflicting ideologies and, more basically, by fear and hate. This is certainly a disorder of psychological origin. Can the term "neurosis" be stretched to include all these millions of sufferers? If so, politicians and sociologists are the doctors, but we hope they will not take to mass treatment by tranquilizers or stimulants, as outlined in Huxley's[23] dreadful prognostication.

Then there is the clearly neurotic anxiety so often described as typical of our epoch (Some wag, in a flash of insight, called it "the aspirin age.") Pathological anxiety certainly is all too common, but it is usually amenable to treatment. The physician, however, sees only that small minority of anxious people who elect to come to him for help. With these he is doing as well as he can, either by being a helpful human being who listens and uses "common sense" or by applying one of the modern techniques of psychotherapy.[24] The ancient medicine

man was a psychotherapist. The Navajo even today believes that many illnesses are caused by being out of tune with nature, and he is often surprisingly successful in using dance, song, and social ritual to cure them.

Our European civilization was building up a well-integrated understanding of physiology and psychology until 1850, when pathology, bacteriology, and chemistry took over the field of medicine and put psychology aside for 60 or 70 years.[25] Of course, there were a few brave souls who upheld the importance of psychogenesis in the understanding of mental and even medical disorders, but they were overwhelmed by the torrent of discoveries in the new medical sciences. World War I suddenly silenced the "scientific" scoffers. Physicians in military service by the hundreds were brought face to face with the reality of psychogenic symptoms: paralysis, blindness, deafness, fainting, palpitations, vomiting, diarrhea, and many other phenomena were recognized as the results of emotional stress. These physicians returned home to lend a much more understanding ear to the teachings of Freud, Janet, Meyer, Prince, and the younger men who were to develop dynamic psychiatry in the next 20 years. This history is now widely known, enlivened as it was with polemics and debased with stubborn prejudices. Most physicians are no longer interested in Krepelin's dogmatic classification-ridden psychiatry. The modern ecological point of view is taking hold of all branches of medicine. One no longer searches for the single cause of a disease but rather for those changing processes in the internal and external environments of an individual person which cause the reaction in him that the physician calls "tuberculosis," "schizophrenia," or "multiple sclerosis." Psychological factors are now usually considered as possibly significant in all diseases and as of undoubted significance in many. The "battle for psychogenesis" [25] has been won.

During this period of enlightenment (1915 to 1940) the most rapidly developing school of psychiatric thought was that of Freud's psychoanalysis. Its influence spread widely in Europe and America. After Freud's death, in 1938, it was to be expected that the leadership would relax and that splinter groups would split off with new attitudes and techniques. This has been to some extent the case; some of the modifications have been useful but none of major importance. Now a new philosophy with its psychiatric implications has gained great popularity in Europe; "existentialism" is widely studied and discussed. Many psychiatrists, notably Binswanger,[26] have developed a form of existential analysis and apply it in psychotherapy. A psychiatric congress in Barcelona, in August, 1958, was devoted almost entirely to existential psychiatry. This movement is of such magnitude that it cannot be ignored. To a considerable extent it accepts Freud's psychoanalysis, but it is no splinter group. Its origins go back to 1840; its philosophical roots are deep,[27] and its use as a therapeutic instrument must be given serious consideration.

In a brief review one cannot give an adequate description of existentialism, but one can sketch its history and its present importance to psychiatry. A book for reference has just appeared in America entitled "Existence: A New Dimension in Psychiatry and Psychology." [28] It is edited by Rollo May, Ernest Angel, and H. F. Ellenberger. Here, in 425 pages, the reader gets in English a good exposition of a complicated subject. The first three introductory chapters, by May and Ellenberger, give a good basis for understanding the more difficult chapters by Minkowski, Straus, von Gebsattel, Binswanger, and Kuhn. Good case histories are given, and existential analysis as a therapeutic procedure is described.

The philosophy of existentialism started with Kierkegaard. He began writing in 1842 and died in 1855. He saw the effect of the

industrial revolution on man, breaking him into a fragmented existence and exaggerating the compartments in the already split life of the Calvinistic European, who was religious on Sundays and worked for money and prestige on weekdays. Industrialism was already making the worker into an automaton with no satisfaction in his labor and no love for the work of his hands. Nietsche, in the 1870's, saw this even more clearly and inveighed against it and against the Victorian mores of repression and respectability. It was left for Freud to understand psychiatrically this fragmentation, repression, and frustration; he developed by his psychoanalysis a method for both investigating and treating those social and personal ills. Binswanger, along with Heidigger, Jaspers, and others, rediscovered Kierkegaad between the wars. In 1942, Binswanger wrote his major work on "Daseinanlyse."[26] He is a psychiatrist who directed a mental hospital in Switzerland; he was an intimate friend of Freud and a member of the Vienna Psychoanalytic Institute. Although he never practiced Freudian psychoanalysis and differed with Freud on many points, he kept Freud's friendship and esteem.

Two paragraphs from May[28] will help to clarify the history of the existential concepts:

Kierkegaard, for his part, foresaw the results of this disintegration upon the inner emotional and spiritual life of the individual: Endemic anxiety, loneliness, estrangement of one man from another, and finally the conditions that would lead to ultimate despair, man's alienation from himself. But it remained for Nietsche to paint most graphically the approaching situation: "We live in a period of atoms, of atomic chaos," and out of this chaos he foresaw in a vivid prediction of collectivism in the 20th century "the terrible apparition—the Nation State—and the hunt for happiness will never be greater than when it must be caught between today and tomorrow; because the day after tomorrow all hunting time may have come to an end altogether—." Freud saw this fragmentation of personality in the light of natural science and was concerned with formulating its technical aspects. Kierkegaard and Nietsche did not underestimate the importance of the specific psychological analysis; but they were much more concerned with understanding *man as the being who represses*, the being who surrenders self-awareness as a protection against reality and then suffers the neurotic consequences (p. 23).

I quote again:

Freud describes the neurotic personality of the late nineteenth century as one suffering from fragmentation, that is from repression of instinctual drives, blocking off of awareness, loss of autonomy, weakness and passivity of the ego together with the various neurotic symptoms which result from this fragmentation. Kierkegaard—who wrote the only known book before Freud specifically devoted to the problem of anxiety—analyzes not only anxiety but particularly the depression and despair which result from the individual's self-estrangement, an estrangement he proceeds to classify in its different forms and degrees of severity. Nietsche proclaims, ten years before Freud's first book, that the disease of contemporary man is that "his soul has gone stale", he is "fed up", and that all about there is a "bad smell—the smell of failure— —.The leveling and diminution of European man is our greatest danger". He then proceeds to describe, in terms which remarkably predict the later psychoanalytic concepts, how blocked intellectual powers turn within the individual into resentment, self-hatred, hostility and aggression. Freud did not know Kierkegaard's work, but he regarded Nietsche as one of the authentically great men of all time (p. 20).

This is all fairly clear, but it might be put into other words: European man began to disintegrate in the 19th century because he allowed his life to become fragmented; he shut off the various parts one from another by a process of pigeon-holing; his religious self did not recognize what his business self was doing; his competitive self did not realize the community feelings he was discarding; his esthetic self was estranged by his dogmas; feeling, affection, and love were minimized in the competitive world. Great repression was needed to avoid seeing one's self; lack of living a harmonious and understanding life led to frustration, anxiety, and aggressive attitudes of defense.

The terminology of existentialism is sometimes overpowering, and the expositions of the philosophy are varied and difficult to grasp. The term *existentialism* itself does not make an illuminating impact. *Dasein* is much better; it has punch and brevity and instills the right connotations.

Although difficult to translate, and perhaps best translated by "being-in-the-world," there is a connotation of participation, reality, and "there you are, what are you going to do about it." "Compartmentalization" is a word much used to denote the process of man's splintering his life; there is perhaps no better word, but it is too much of a mouthful for most people. It might be clearer to use the figure of man as a wholesome unit, the *vir integer*, with integration as health and disintegration as sickness.

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News and Comment

ANNOUNCEMENTS

International Goiter Conference.—The Fourth International Goiter Conference will be held July 5-9, 1960, in London, England, under the auspices of the London Thyroid Club and the American Goiter Association. The American Goiter Association plans to make available to worthy candidates a limited number of travel grants for participants of this meeting. Applications are available from John C. McClintock, M.D., 149½ Washington Ave., Albany 10, N. Y. Applications will be received until Jan. 1, 1960.

Contributions of Basic Science to Modern Medicine

The Experimental Approach to the Mechanism of Fever

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Fever may be defined as any abnormal elevation in body temperature. Although abnormal elevation of body temperature is sometimes a reflection of normal physiological processes, such as exercise, consumption of food, menstruation, and pregnancy,[1] it is properly designated as fever only when it is a manifestation of disease. The investigations of Wunderlich[2] first placed clinical thermometry on a firm basis, and his findings formed the nucleus of a large body of empiric knowledge concerning fever as a manifestation of disease. Despite the fact that much is known about fever from the clinical point of view, the mechanisms responsible for this important physiological disturbance are poorly understood. It is the purpose of this report to summarize the results of experimental studies on the pathogenesis of fever.

Relationship of Fever to Tissue Injury

Many widely diversified pathological entities are associated with fever. Among these are infections; "collagen-vascular diseases," such as rheumatoid arthritis and lupus erythematosus; neoplasms; blood dyscrasias, such as leukemia; metabolic aberrations, such as gout, porphyria, and thyrotoxicosis; hypersensitivity states, such as serum sickness, and processes involving necrosis of tissue, of which infarctions of the myocardium or lung are good examples. Some bacteria and a few viruses possess intrinsic pyrogenic properties, but these cannot be implicated in the etiology of most diseases. This implies that fever involves a response of the host that is common to diseases of many types. The obvious common denominator in the pathogenesis of fever is *injury* to tissue, and it is often stated, without proof, that tissue injury causes fever. One logical approach to this hypothesis has been to test the ability of injured cells or extracts of damaged tissue to cause fever.

Fever-Producing Substances in Sterile Exudates

The concept that fever is a consequence of tissue breakdown was introduced by Dickinson, in 1785, and during the 19th century a number of European investigators demonstrated that intravenous administration of pus or necrotic tissue resulted in fever.[3] In 1945, Menkin isolated a fever-producing euglobulin from canine exudates produced by intrapleural instillation of turpentine. This material, which he termed *pyrexin*, produced fever in rabbits and dogs when administered intravenously and was postulated to be the active humoral mediator of fever associated with inflammation.[4] There is reason to believe, however, that the fever produced by Menkin's material was largely a result of introduction of extraneous pyrogenic contaminants during the process of purification.[5]

Bennett confirmed Menkin's observation to the extent of finding a pyrogen in unfractionated sterile chest fluids of dogs given turpentine intrapleurally.[6] However, the injection of this material into test animals produced only single-peaked, relatively brief fevers, in contrast to the double-

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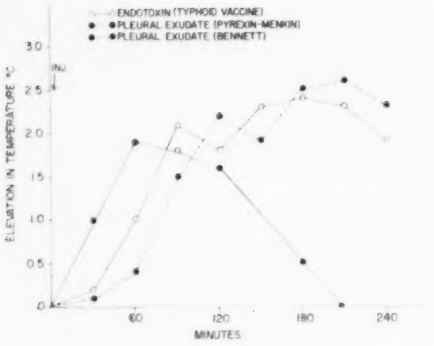

Fig. 1.—The febrile response of rabbits after administration of bacterial endotoxin, pyrexin, and sterile pleural exudate.

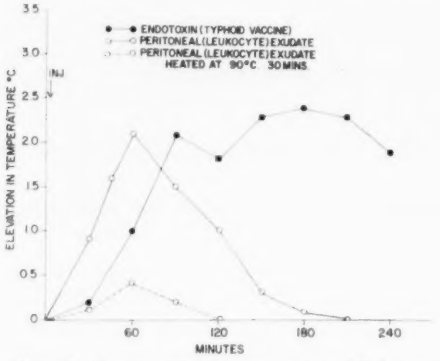

Fig. 2.—A comparison between the rabbit's temperature after injection of typhoid vaccine and sterile peritoneal exudate, heated and unheated.

peaked, prolonged fevers associated with Menkin's pyrexin and with bacterial pyrogens (Fig. 1). Bennett also showed that the pleural exudates did not become pyrogenic for test animals until the fever in the donor dog had subsided, raising the possibility that the donor's fever was not a result of simple absorption of fever-producing substance from the exudate.

Bennett and Beeson were able to demonstrate a fever-producing substance in whole granulocytes, leukocyte extracts, and sterile peritoneal exudates in rabbits.[3] These preparations produce a fever of rapid onset and brief duration when injected intravenously into normal rabbits. Their activity is destroyed when they are heated at 90 C for 30 minutes, differentiating them from bacterial pyrogens which withstand heating and autoclaving (Fig. 2). These tissue pyrogens also differ from bacterial pyrogens and Menkin's pyrexin in their inability to evoke tolerance by repeated injection (see below) and to elicit leukopenia. The Table summarizes the properties of these and several other pyrogenic substances.

Although many tissues have been examined, polymorphonuclear leukocytes are the only cells thus far found to contain a substance capable of eliciting fever. It is nonetheless possible that other tissues contain pyrogenic factors. Evidence for this is the finding that exudates obtained from animals made granulocytopenic with mechlorethamine hydrochloride (nitrogen mustard) are pyrogenic.[5] However, no pyrogens have been extracted from the tissues of leukopenic rabbits.[7]

Recent experiments suggest that tissue pyrogens may be species-specific and that

Biological Properties of Various Pyrogens

	Bacterial Endotoxins	Pyrexin	Sterile Inflammatory Exudates	Endogenous Serum Pyrogen	Influenza Viruses
Duration of fever	Prolonged	Prolonged	Brief	Brief	Prolonged
Latent period, min.	45-60	45-60	15	15	2 hr.
Leukopenia in recipients	Marked	Marked	None	Slight	Lymphopenia only
Tolerance evoked by repeated administration	Yes	Yes	No	No	Yes, on 2d day
Fever in tolerant recipients	No	No	Yes	Yes	No
Inactivated at 90 C for 30 min.	No	No	Yes	Yes	Yes
Produces endogenous circulating pyrogen	Yes	?	No	± *	Yes

* Endogenous pyrogen obtained after administration of virus is capable of inducing further release of endogenous pyrogen.[11]

exudates from rabbits are thermogenic only for that species whereas those produced in dogs cause fever only in canines and are nonpyrogenic for rabbits.[8] Finally, an essential role of leukocytic pyrogen in the fever of disease remains to be demonstrated. Rabbits with sterile peritoneal exudates (which produce fever when injected into recipient animals) are not themselves febrile.[9] Despite these discrepancies, discovery of the existence of pyrogenic substances of endogenous origin lends credibility to the general concept that tissue injury is the process underlying the development of fever.

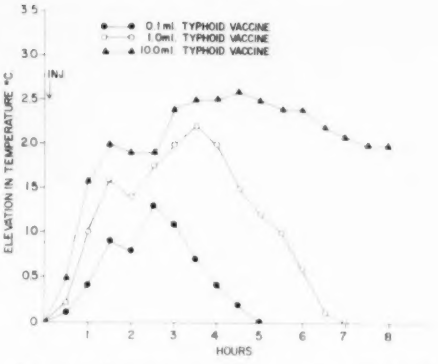

Fig. 3.—Characteristic fever curves produced with various amounts of typhoid vaccine in dogs.

Fever Due to Bacterial Endotoxins and Pyrogens

Many bacteria, particularly Gram-negative species, possess endotoxins or toxic somatic antigens. These are lipopolysaccharides of high molecular weight. Among many other physiological alterations, they can produce high fever when injected into man and animals and therefore have been termed *bacterial pyrogens*. These substances, of which ordinary typhoid vaccine is a prime example, are convenient for the study of experimental fever.

Characteristics of Bacterial Pyrogen Fever [10]

A. Latency and Duration.—When a bacterial endotoxin is administered intravenously to experimental animals or man there is a 30- to 60-minute delay before the initial abrupt increase in temperature. This first rise is followed by a transient fall and then a secondary peak, producing the biphasic response that is characteristic of endotoxin fever. After ordinary doses fever persists from four to six hours but may be much prolonged by administration of large quantities (Fig. 3).

B. Changes in Leukocytes.—Intravenous administration of bacterial pyrogens is associated with a profound transient leukopenia, followed one or two hours later by marked leukocytosis. The sudden fall in leukocytes subsequent to administration of bacterial endotoxins is presumably the result of injury to these cells by the toxin, although no direct evidence for this is available. It is not clear that the leukocytes undergo any functional alterations when they leave the circulation; it is known that they are sequestrated in the capillary beds of various organs, such as the lung.

C. Tolerance.—It has long been noted by clinicians employing vaccines for fever therapy that patients become resistant to the action of the vaccine and that, as therapy progresses, larger and larger doses are required to obtain an adequate systemic effect.[10] In studying this phenomenon, Beeson demonstrated that rabbits become refractory to the fever-producing action of endotoxins when the same amount of toxin is administered daily[11] (Fig. 4). This resistance to bacterial pyrogens, which has been termed *tolerance*, appears within four to five days and remains constant until cessation of daily injections, after which it subsides gradually and disappears after about three weeks. Tolerance is nonspecific, and animals resistant to endotoxin from one type of organism are also refractory to those from heterologous bacterial species. Tolerance is independent of specific antibodies in the serum and does not seem to be related to the usual mechanisms of immunity.

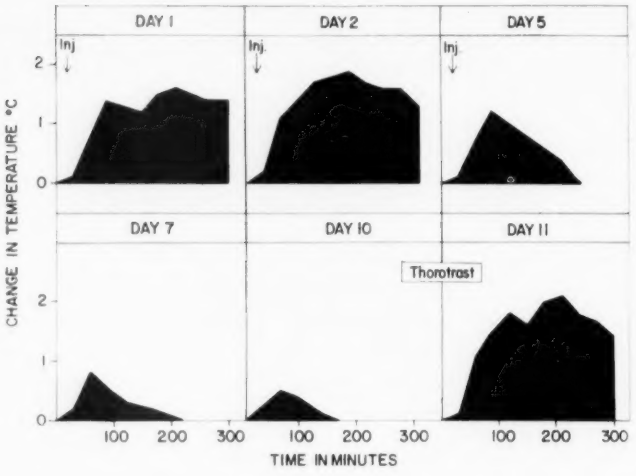

Fig. 4.—The phenomenon of tolerance to the pyretogenic action of 1.0 ml. of typhoid vaccine in rabbit. Colloidal thorium dioxide (Thorotrast) completely reversed the refractory state.

Tolerance can be abolished by the administration of reticuloendothelial "blocking" agents, such as colloidal thorium dioxide (Thorotrast) or trypan blue; tolerant animals given these materials are again fully susceptible to the pyretogenic action of the toxin.[12] This finding has led to the thesis that during the tolerant state injected endotoxin is removed more rapidly from the circulation, with consequent diminution of tissue injury and fever. "Blockade" of the reticuloendothelial system interferes with clearance of endotoxin, and the body tissues are again liable to maximal injury and fever.

Two final points about tolerance deserve comment. A *completely* resistant state is never achieved no matter how long daily administration of endotoxin is continued.[13] It should be emphasized that tolerance is a relative, dose-dependent phenomenon and that animals made refractory by daily injection of a small dose of a bacterial endotoxin will respond with high fevers when challenged with a larger amount.[14]

Relationship of Tissue Injury to Fever of Bacterial Endotoxins

A. Endogenous Serum Pyrogen.—In 1947, Beeson suggested that the long latent period between administration of endotoxins and onset of fever might mean that these substances did not act directly upon the temperature-regulating centers of the brain.[11] It was further suggested, by Atkins and Wood, that the latent period was the time required for the endotoxin to injure tissue, with resultant release of a secondary factor of endogenous origin which then acted on the nervous centers to produce fever.[15]

In experiments designed to demonstrate this endogenous factor, Atkins and Wood gave typhoid vaccine to rabbits and bled them at intervals, finding that two different pyretogenic substances appear in the serum. The first is present in maximal concentration up to 5 minutes after administration of the vaccine and when tested in normal animals produces a prolonged fever which occurs after a 30- to 45-minute latent period. In tolerant recipients, however, this substance is inactive, evidence that it is the originally administered vaccine. A second fever-producing substance appears in the serum about one hour after injection of the vaccine and persists for two hours thereafter; it is usually present in maximal concentration 120 minutes after administration of the bacterial toxin. This substance, which has been termed *endogenous pyrogen*, produces a brief, monophasic fever after a short latent period in normal *as well as tolerant*

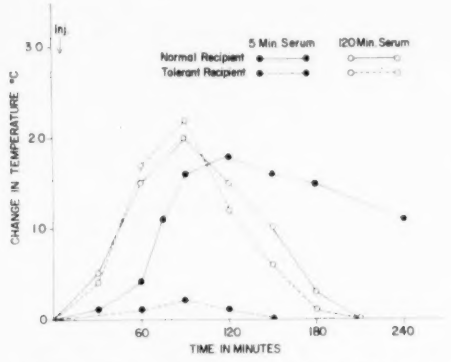

Fig. 5.—The pyrogenicity of 5-and 120-minute serum pyrogen in do . Note that serum obtained five minutes after a ministration of endotoxin is inactive in tolerant animals, proof that it is the endotoxin originally injected.

recipients (Fig. 5).[15,16] This implies that it is different from the endotoxin originally administered, and many studies attempting to compare endogenous pyrogen with endotoxin (or five-minute serum) have demonstrated that endogenous and exogenous pyrogens have markedly different biological properties (Table).[14,17] The presence of endogenous serum pyrogen after administration of endotoxin has been confirmed in the dog by use of a number of different vaccines and purified endotoxins.[14]

B. Relationship of Endogenous Serum Pyrogen to Other Tissue Pyrogen.—In a previous section, the thermogenic properties of leukocytic exudates were described. These substances produce fever which appears after a short latency, and is monophasic and of brief duration. The activity of the exudates is destroyed by heating at 90 C for 30 minutes. Endogenous serum pyrogen produces a similar fever and is also heat-labile.[18] Both substances are capable of producing fever in endotoxin-tolerant animals, and daily administration does not result in lessened ability of an animal to react. The observation that the profound leukopenia associated with the administration of bacterial endotoxin invariably precedes fever and the appearance of endogenous pyrogen in the serum lends support to the idea of Atkins and Wood that endogenous pyrogen is a product of damaged cells, as does the finding that polymorphonuclear leukocytes release endogenous pyrogen into the cell-free fluid of inflammatory exudates in vivo and in vitro.[18] Finally, the inability of dogs made leukopenic with mechlorethamine hydrochloride to elaborate endogenous pyrogen is further indication that the polymorphonuclear leukocyte is an important source of endogenous serum pyrogen.[14]

C. Role of Endogenous Pyrogen in Fever Caused by Bacterial Endotoxins.—Although it has been convincingly demonstrated that an animal given bacterial endotoxin releases a substance into the circulation which is capable of producing fever in *another* animal, it does not necessarily follow that this endogenous fever-promoting substance is the only mechanism responsible for the fever in the donor. It is tempting to assign the responsibility for fever solely to endogenous pyrogen, but there are a number of observations which indicate that the mechanism of endotoxin fever is a more complex one. These may be summarized as follows:

1. An animal given repeated daily doses of endotoxin never becomes completely tolerant, and some degree of fever is always demonstrable. This remnant of fever occurs in the absence of demonstrable amounts of circulating endogenous pyrogen.[20]

2. Dogs rendered granulocytopenic with mechlorethamine hydrochloride respond to administration of bacterial endotoxins with high fever despite inability to elaborate endogenous serum pyrogen.

3. Direct intrathecal administration of a tiny amount of endotoxin results in an enormous elevation in body temperature, which is not associated with leukopenia (Fig. 6) or the release of circulating serum pyrogen. Furthermore, repeated daily instillation of endotoxin into the subarachnoid space is not followed by resistance to the thermogenic stimulus. These experiments strongly suggest that bacterial pyrogens are

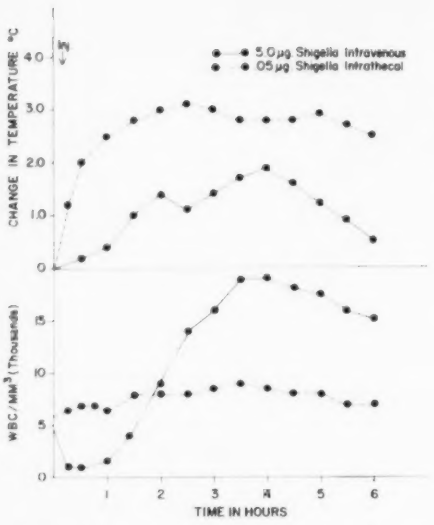

Fig. 6.—The effect of intravenous and intrathecal endotoxin on body temperature and white blood cells in rabbits.

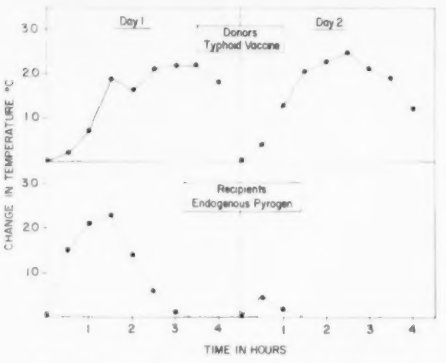

Fig. 7.—The dissociation between tolerance to the thermogenic effect of bacterial endotoxin and the depletion of endogenous pyrogen. While there is no diminution of fever on the second day, endogenous pyrogen has virtually disappeared from the circulation.

capable of acting directly on the thermoregulatory centers to produce fever.[20]

4. There is temporal dissociation between the development of tolerance to the fever-producing action of endotoxin and endogenous pyrogen production. While animals take five to seven days to become resistant to the pyretogenic effect of endotoxin, endogenous serum pyrogen in demonstrable amounts is absent after only two successive daily injections. Furthermore, if dogs are given doses of endotoxin sufficiently large to suppress the development of tolerance, high fever occurs in the absence of circulating pyrogen (Fig. 7).[17]

5. It has been mentioned previously that endotoxin fever is biphasic. During the development of tolerance the second peak disappears first. This coincides with the failure of endogenous pyrogen to appear in the circulation. Both the second peak and endogenous serum pyrogen reappear when colloidal thorium dioxide is administered or when a larger dose of endotoxin is given

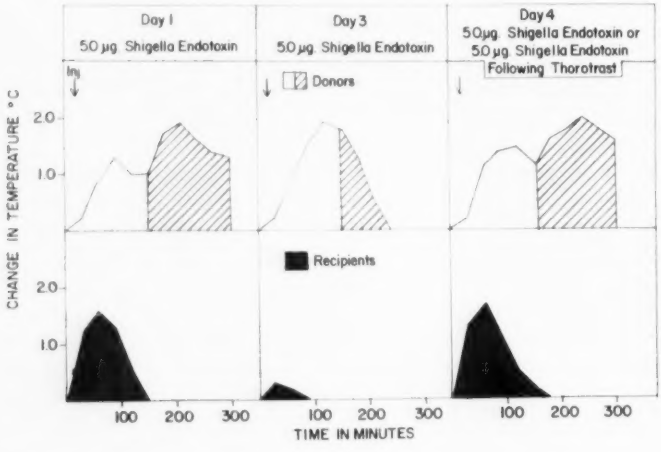

Fig. 8.—The relation of endogenous pyrogen in the circulation and the second hump of the temperature curve. Note that both colloidal thorium dioxide and larger doses of endotoxin elicited the reappearance of endogenous pyrogen as well as the second peak.

(Fig. 8).[17] The "depletion" of endogenous pyrogen could be a result of rapid clearance of endotoxin from the circulation, preventing tissue injury and the release of the secondary fever-promoting substance. When colloidal thorium dioxide or larger doses of toxin are employed, the host's defenses are overwhelmed and tissue injury again occurs. These experiments indicate that endogenous pyrogen is probably responsible for the second febrile peak but that the early phase of fever is largely independent of the endogenous factor.

We interpret the present evidence to favor the hypothesis that *endotoxin* fever is mediated by two distinct mechanisms: (*a*) a *direct* action of the toxin in the brain and (*b*) the action of toxin on cells, resulting in release of endogenous pyrogen. The finding of a pyrogenic substance indistinguishable from bacterial endotoxin in the cerebrospinal fluid within 15 minutes after intravenous injection of toxin may be cited as further evidence for the direct action of endotoxin.[20]

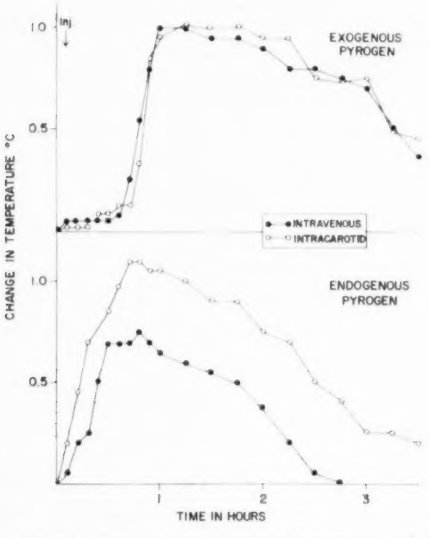

Fig. 9.—Comparison of the intravenous with intracarotid administration of endogenous and exogenous pyrogen. Endogenous pyrogen was more pyrogenic when given by the intra-arterial route; this difference was not noted when exogenous pyrogen was administered.

King and Wood, on the other hand, subscribe to the thesis that endogenous pyrogen acts directly on the brain and is the sole factor responsible for fever caused by bacterial endotoxins.[21] When they infused endogenous or leukocytic pyrogen into the carotid artery of rabbits at an appropriate rate they obtained a febrile response of more rapid onset and greater magnitude than when these substances were administered intravenously. In contrast, endotoxin suspended in serum elicited the usual fever curve, characterized by a long latent period and a double hump by either route (Fig. 9). These findings were interpreted by them to mean that endogenous pyrogen directly produced a greater febrile response when given intra-arterially, whereas endotoxin, acting by a less direct mechanism, produced the same amount of fever regardless of the route of administration. These experiments, however ingenious, are sufficiently complex to require caution in interpretation. Granted that endogenous serum pyrogen, *once it has appeared* in the circulation, may affect cerebral centers more readily than circulating endotoxin, it is to be remembered that endotoxin is *always present in the blood before* the endogenous pyrogen appears. This head start could well make up for the fact that penetration into the nervous system is slower for the large lipopolysaccharide endotoxin than it is for the endogenous substance when they are infused at equal rates.

Other Experimental Fever and Its Relation to Endogenous Pyrogen

A. Viruses.—Viruses of the Newcastle-influenza group are capable of producing fever in rabbits when administered intravenously. The temperature response to virus is characterized by a long latent period and a double hump (Fig. 10*A*).[22] Animals rapidly acquire tolerance to virus and respond with little or no fever to the same dose given on the day after the initial injection (Fig. 10*B*).[23] Virus fever is also associated with a transferable endogenous

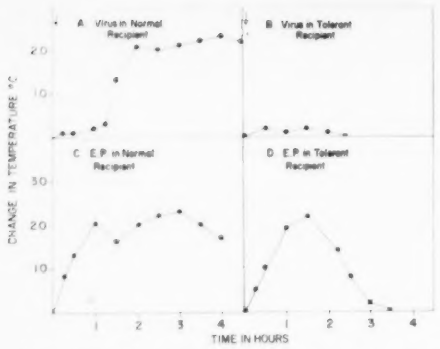
A. Virus in Normal Recipient
B. Virus in Tolerant Recipient
C. E.P. in Normal Recipient
D. E.P. in Tolerant Recipient
CHANGE IN TEMPERATURE °C
TIME IN HOURS

Fig. 10.—Fever elicited by virus and virus-induced endogenous pyrogen in normal and virus-tolerant recipients.

serum pyrogen, which produces a biphasic rise in temperature when administered to normal recipients (Fig. 10C).[24,25] The magnitude and duration of the fever in the normal recipient is remarkably similar to that observed in the donor after administration of virus. As might be expected, tolerance to the pyrogenic action of virus is accompanied by disappearance of endogenous pyrogen from the circulation.

The biphasic fever following administration of virus-induced endogenous pyrogen has aroused particular interest. Atkins postulates that the initial peak may be related to the direct action of the pyrogen on the thermoregulatory centers, while the second hump probably represents a second release of endogenous pyrogen. In other words, endogenous pyrogen per se may serve as the stimulus for further release of endogenous pyrogen.[25] However, when rabbits are made tolerant by a previous injection of virus the second febrile peak fails to appear and the response to endogenous pyrogen is monophasic (Fig. 10*D*).[26] Under these circumstances, the virus administered on the previous day may have exhausted the animal's endogenous pyrogen stores, rendering it incapable of further release of its fever-producing substance. It appears, therefore, that, in contrast to endotoxins, fever produced by viruses is entirely dependent upon the release of endogenous pyrogen. Presumably the active thermogenic substance in the serum of animals made febrile with virus is also a product of tissue injury. It has been shown that it is not a remnant of virus particles or antibody evoked by administration of virus. The absence of granulocytopenia in virus fever implicates cells other than polymorphonuclear leukocytes as precursors of endogenous pyrogen.

B. Hypersensitivity Reactions.—Stetson described fever and leukopenia following administration of tuberculin to hypersensitive rabbits; normal rabbits remained afebrile.[27] Rabbits sensitized to bovine albumin also develop fever when challenged with the protein one week later.[28] Transferable pyrogen is reported to be present in the serum of these animals.[13] Whether this endogenous pyrogen is related to the formation of specific antibody or is a nonspecific response to tissue injury is presently under investigation.

C. Pneumococcal Infections.—Pneumococci do not possess endotoxins and are normally nonpyrogenic when injected directly into the blood stream. When this organism is instilled into the peritoneal cavity of rabbits, however, the animals become febrile within six to eight hours after the infection is initiated.[29] At the time of appearance of the fever, inflammatory exudate from the peritoneum becomes pyrogenic for recipient rabbits. These exudates are identical to those obtained from granulocytes or sterile inflammations, as described in the first section. They produce brief, single-peaked fever, are inactivated by being heated at 90 C for 30 minutes, and are pyrogenic for animals tolerant to bacterial endotoxin (Table). Lymph collected from these animals is also capable of producing fever in normal rabbits. Recently King and Wood have been able to demonstrate a transferable pyrogen in the blood of these animals.[30] Treatment of these rabbits with penicillin rapidly aborts the infection; the animals become afebrile, and the peritoneal exudate loses its fever-promoting capacity. This is the only in-

stance in which the presence of fever in the host has coincided with the appearance of a tissue pyrogen at the site of an inflammatory process and in which it has been conclusively demonstrated that the tissue pyrogen enters the circulation and presumably gains access to the thermoregulatory centers in the brain.

D. Streptococcal Infections.—When lysates of Group A β-hemolytic streptococci are administered to normal rabbits intravenously, a prolonged double-peaked fever occurs. Repeated injections evoked tolerance to the lysates, and some degree of cross tolerance with the toxins of Gram-negative bacteria also exists.[31] Atkins has reported that fever secondary to intrapharyngeal inoculation of hemolytic streptococci in rabbits is associated with the presence of a circulating pyrogen, presumably released from endogenous sources.[32] King and Wood have also demonstrated a circulating pyrogen in animals with experimental streptococcal cellulitis.[30] Although the transferable pyrogen associated with streptococcal infection appears to be biologically similar to that seen after pneumococcal infection, the demonstration that streptococci contain an endotoxin suggests that the mechanism of endogenous pyrogen production in these two infections may differ.

Role of Endogenous Pyrogen in Fever

It would be most gratifying if the data at hand permitted the conclusion that fever, regardless of cause, is associated with the release of endogenous pyrogen. Unfortunately, such is not the case. As has been pointed out in a previous section, bacterial endotoxins are capable of producing fever in the absence of demonstrable endogenous pyrogen. Fever occurs after administration of chemical agents such as dinitrophenol, lysergic acid diethyl amide, and kaolin in the absence of endogenous pyrogen, in spite of the fact that these agents most surely provoke injury to tissue.[14] Placement of bacterial pyrogens directly into the subarachnoid space results in a prompt rise in temperature, but no endogenous pyrogen is detectable after this strong pyrogenic stimulus. At this writing, only in the fevers associated with pneumococcal infection and with injection of influenza viruses has production of endogenous pyrogen appeared to be the sole mechanism of elevation of temperature. On the other hand, there is good evidence that fever associated with the toxins of Gram-negative bacteria can be to a large degree independent of the endogenous pyrogen mechansim.

Nature of Endogenous Pyrogen

Although much has been done to characterize endogenous serum and tissue pyrogens biologically, all attempts to elucidate the biochemical properties of these substances have ended in failure. This is due largely to the ubiquity of bacterial pyrogens which contaminate almost all attempts at chemical manipulation. Therefore, one can only speculate on the origin and exact character of these substances. It is conceivable that endogenous pyrogen associated with administration of bacterial endotoxin is nothing more than the toxin originally administered which has been modified by the plasma or its components. Grant and Whalen demonstrated that bacterial endotoxins incubated with rabbit serum or plasma are capable of eliciting a febrile response not associated with the long latent period commonly seen after administration of endotoxin alone.[33] These observations were confirmed in humans by Snell et al., who found that bacterial pyrogen incubated with serum produced a monophasic fever of rapid onset and that, unlike bacterial pyrogen, this substance was heat-labile and non-dialyzable and did not evoke tolerance after repeated administration.[34] In short, the endotoxin-serum mixture behaved biologically like endogenous rather than exogenous pyrogen. Whether this combination occurs in vivo remains in doubt. Certainly the rapid disappearance of radioactively labeled endotoxin from the blood stream after its intravenous administration suggests that en-

dogenous pyrogen is a substance distinct from bacterial toxin.[35] In addition, the endogenous pyrogen seen in association with the administration of viruses or pneumococci is not related to the pathogenic activity of these agents or to formation of specific antibody to them. The recent discovery by Landy and Shear[36] that tissues of various plants or animals contain lipopolysaccharides which elicit biological reactions similar to those produced by bacterial endotoxins lends itself to an attractive hypothesis. Varied stimuli, such as bacterial endotoxins, viruses, or pneumococci, may serve merely to liberate naturally occurring endotoxin-like materials into the circulation. Suffice it to say that much more work must be done before this speculation can be substantiated or related more definitively to the fever of hypersensitivity, inflammation, or infection.

Comment

As with most research, the investigations described in this brief report raise more questions than they answer. However, they also serve to arouse interest in a common biological phenomenon, which may eventually lead to a better understanding of the complicated processes of the body's response to the stresses of disease.

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Books

EDITED BY WILLIAM B. BEAN, M.D.*

Pathology for the Physician. By William Boyd, M.D. Price, $17.50. Pp. 900, with many excellent illustrations. Lea & Febiger, 600 S. Washington Sq., Philadelphia 5, 1958.

Minor incidents, events, and episodes plant the seeds for later developments which furnish direction, pleasure, and instruction in a medical career. In 1931, during the summer after my first year in medical school, my father put in my hands a book called "The Pathology of Internal Disease," by William Boyd. He said that it had pleased him greatly. Ergo, I should read it. This injunction was obeyed for I had come, perhaps reluctantly, to admire my father's canny judgment. Perhaps today I should say we shared certain tastes. At any rate, having wrestled with the massive tomes of anatomy, histology, and embryology, I was pleased to have a chance to preview what I looked forward to as an introduction to the more clinical aspects of medicine, even if it was only the residue found in pathology. To my great delight, I found Boyd's book not only full of new wonders and mysteries but written in such a charming style that its manner, as well as its matter, made any feeling of work or filial duty vanish. Later during the second year of medicine, an occasional quotation I made from Boyd enabled me to win an undeserved reputation as a sophomore oracle.

Several years ago it was great good fortune to spend several days with Dr. Boyd and to share a place with him on the same program. Thus I had an opportunity to gain more than casual acquaintance with one of my medical heroes. And so it was with more than ordinary interest that I set about examining Boyd's latest book, "Pathology for the Physician." It is an offspring of the first book rather than the same book grown older. Though it is older and perhaps wiser, it is just as delightful. In the early edition an effort was made to relate symptoms to lesions. The present book carries the story further. It deals with the altered processes which create both symptoms and lesions as well as the altered function inherent in altered structure. Thus the book is more than a text of pathology. It really is a connecting link, uniting several approaches to our understanding of sick people.

Enormous changes have occurred in the period of nearly thirty years since I read the first edition. They have revolutionized the face of pathology as well as the face of medicine. There has been some suspicion that the pathology of the dead house might not any longer be a valuable discipline or a source of new or useful knowledge. Perhaps there is a bias in Starr's preference for using cadavers for necrophysiological studies of ballistocardiology. Even the novice senses that pathology and autopsies still have great medical importance. Boyd has illustrated elegantly in this book one thesis, that comprehension of the morphology of disease is essential to a clearer understanding of what goes on within the body, the organ, and the cell. Without it one deals, or at least runs the risk of dealing, in medical dialectics.

As is to be expected of such a comprehensive book, there is some unevenness. But in looking up any reference it is easy to see that a tremendous effort was used to bring the book well up to date. It includes things published the month it went to press, clear testimony to the enthusiastic energy of the author.

No one can understand internal medicine without understanding pathology. A reference book of some kind is essential. Boyd's "Pathology for the Physician" fills this need extremely well. This book presents pathology as a living, dynamic discipline by relating process to structure and malfunction to symptoms in the same way that an archeologist from a few shards and artifacts reconstructs the ways and customs of an entire nation now ancient and defunct. Such arts of scholarship help us to understand ourselves. This book is a fitting capstone to Dr. Boyd's distinguished contributions to the art, as well as the science, of pathology, medicine, and living people.

WILLIAM B. BEAN, M.D.

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Vascular Spiders and Related Lesions of the Skin. By William Bennett Bean, M.D. Price, $8.50. Pp. 372, with 130 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

When William Bean takes pen or dictaphone in hand, we are accustomed to expecting something refreshing and original—and painlessly enlightening. His new book "Vascular Spiders and Related Lesions of the Skin" will disappoint none of his admirers. In an age devoted to gadgetry, graphs, and statistical analysis, the bewildered physician who once thought that history taking and careful physical examination constituted his major diagnostic obligations will find comfort and illumination in this straightforward account of observations made at the bedside and in the clinic by a sympathetic and perceptive doctor. That the account was written in the first person by a philosophical and literate physician is a fortunate circumstance, for the happily chosen words that add so much charm to the reading always embellish and never obscure the important things the author has to impart.

The researches detailed here began more than twenty years ago with the eager curiosity of an inquiring mind regarding commonplace lesions of the skin seen in patients with cirrhosis of the liver and in pregnancy. Finding no ready explanation for vascular spiders from his teachers or ordinary medical texts, Dr. Bean began painstakingly to make his own records, detailing the accompanying clinical data which he thought might be pertinent. Naturally a keen interest in other vascular lesions of the skin developed and with it the conviction that many were interrelated. As the study of patients progressed, his grasp of the available knowledge from other sources enlarged. The present book contains 943 references, many of which were original descriptions of the clinical phenomena being discussed and many of which are quoted freely. One has the impression that the author really read all of these papers and books—and countless others. A lively correspondence with other physicians interested in this field proved stimulating and rewarding. The fruits of this exchange with other careful observers are passed on to the reader. It is characteristic of the author that, after marshaling a noteworthy body of evidence in support of his hypothesis that estrogenic and related hormones are a major factor in causing spiders to appear, he immediately points out the flaws in the argument. Lesions occur in men and women equally and in boys and girls before puberty and in women after the menopause. He states that the humoral mechanism can not explain localization but, of course, also, does not discredit it. The section on spiders ends with this statement, "In short, the observations are on much firmer ground than the hypothesis, and this is good."

The book goes on to explore the wonders of the skin manifestations of metastatic carcinoid, the skin lesions of pellagra and scurvy, all of the congenital and hereditary lesions and birthmarks that result from the anarchy of the blood vessels that reach and involve the skin, functional flushes, neoplastic vascular lesions, traumatic vascular lesions, and a great variety of other anomalies. The chapter on vascular lesions which increase with aging is very comforting. We are told to reassure our patients who have cherry angiomas, venous stars, venous lakes, and caviar lesions under the tongue. They are average accompaniments of growing older and in themselves do not shorten life.

All of the contents of this remarkable book should not be even listed, for that would spoil the fun. It is a fairly safe prediction that no reader who dips deeply into this exciting account of the remarkable and variegated phenomena which lie in the skin of his patient directly under his gaze can return to his clinical duties with quite the same complacency he had before. He can not salve his conscience with the rationalization that modern technical advances which have come since his time make research the exclusive business of his younger and more fortunate colleagues. Here are detailed important data gathered simply by looking at the patient, finding out as much of his physical problems as purposeful questioning and correlative examination will disclose, and recording the observations in an orderly manner. Any physician has the opportunity to do as much. It is significant that no subject in the book is covered by "a review of the literature" alone. This is done in each category, but the important matter is what the author has observed for himself.

Mixed with the clinical observations are numerous gems which could come only from the pen of the wise physician who *thinks* about what he sees. For instance, in concluding a short discussion of the ridiculous notion once held that cherry angiomas were in some way related to underlying cancers, he has this to say: "The need once more to exorcise the ghost of cancer illustrates the ratio between the small work of making a positive but wrong assertion and the effort needed to demonstrate its invalidity, since science can never prove a negative. Some one

with authority and enthusiasm makes an uncontrolled observation, or an eager assistant makes it for him. It becomes enmeshed in what with innocent euphemism we call 'the literature.' It carries the mystical potency of the written word in an age when mere literacy exposes the uncritical to the hazard of believing what they read. No one has calculated the countereffect, the sad series of negative reports needed to bury the error. No doubt it will crop up again."

The volume contains a few typographical errors, which probably made the author squirm, but there are no more than in most books. Two pages of good color photographs appear in the front, and a great many diagrams and good black-and-white photographs illustrate the subsequent portions. They seem somewhat pallid compared to the authoritative and beautifully written subject matter which they accompany. Both the clinician and the laboratory worker are urged to read this book through. All who do so will be enlightened, stimulated, and gently chastened.†

PAUL S. RHOADS, M.D.

Coccidioidomycosis. By Marshall J. Fiese, M.D., F.A.C.P. Price, $7.50. Pp. 253, with 40 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

Finding a loose human head, a hand, and a foot a half-century old, lying around a pathology department, is a strange event, but identifying them, too boot, is unusual indeed. This little anecdote about Posadas and Wernicke's original case of coccidioidomycosis and other stories add to the interest of this detailed monograph. The author has a gift for teaching, and he has outlined the now considerable amount of knowledge of this disease with the tongue-twisting name. The purpose of this book is best expressed in Dr. Fiese's own words.

"We are often faced with the paradox of intimate acquaintance with a disease and embarrassing confusion about its cure. . . .

"It will be thus with fungus *Coccidioides*. The meager therapeutic results already achieved at least demonstrate that coccidioidomycosis is not necessarily incurable. Because coccidioidal disease has heretofore been mainly of regional interest, research concerning its therapy has not always had high priority. Were it as ubiquitous as lobar pneumonia or poliomyelitis, the answer would already be at hand. With the expanding population of the Southwestern States and the increasing interest in fungus diseases throughout the nation, research concerning coccidioidal disease will be intensified and a definitive means of therapy will sooner or later be found."

The publisher has done an excellent job in producing a very pleasing book, but the book might have been published by the University of California Press or by the Stanford University Press as a memorial to the pioneers in that field from the faculties of these universities, Drs. Emmet Rixford, William Ophuls, Herbert Moffit, Douglass Montgomery, Jean V. Cooke, Ernest Dickson, Charles E. Smith, Alvin J. Cox, Harold K. Faber, and many others. It is interesting that, as investigators and as experimental animals, medical students have added to the knowledge of this disease as they have to the understanding of other diseases.

What was once a rarity is now common in California, Arizona, Texas, and New Mexico. The primary infections in these areas total about forty-five thousand each year. The fungal parasites of the soil are of such tiny dimensions that they are carried by the slightest breeze and are inhaled with ease. As in tuberculosis, a primary disease with systemic sensitization is usual, but rarely a disseminated disease of many organs may follow.

The book summarizes our knowledge of coccidioidomycosis and provides an exhaustive bibliography. If you are an internist, phthisiologist, public health worker, or thoracic surgeon, this will be a welcome addition to your library.

IAN MACLEAN SMITH

Alcoholism. By Arnold Z. Pfeffer, M.D. Price, $6.50. Pp. 98, with 3 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1958.

Lieut. Col. Gregory Boyington of the U. S. Marine Corps shot down twenty-six Japanese planes in World War II. He was dauntless in action and subsequently in prison camp, won the Medal of Honor and the Navy Cross, and was an alcoholic. He now no longer drinks. Readers of his recent autobiography, "Baa Baa Black Sheep," may deduce that a man may be an alcoholic and yet be skilled, fearless, and resolute. Not all alcoholics

† Approved with considerable pleasure and no mock modesty.

W. B. B., book review editor.

are failures, who cower from the cold gray world. What explains our attitude toward alcoholics? Some physicians think that the prognosis is hopeless. This is not so; thirty to fifty percent of patients cease drinking. Perhaps the core of our disregard is the idea that drinkers rarely want to be treated. Most patients want us to help. This makes us feel better or more important, emotions not to be discounted except in public. The excellent book under review deals with the problem drinker in industry and is commended to all physicians working in this field. In industry, the patient's motivation can be arranged, for companies can make an employee wish to stop drinking by the threat of being fired and by friendly support if the employee accepts treatment. The approach succeeds in industry and might be extended.

DANIEL B. STONE, M.D.

Practitioners' Conferences Held at New York Hospital-Cornell Medical Center. Vols. 5 6. Edited by Claude E. Forkner, M.D., F.A.C.P. Price, $6.75. Pp. 396 and 378, with 55 (Vol. 5) and 20 (Vol. 6) illustrations. Appleton-Century-Crofts, Inc., 35 W. 32d St., New York 1, 1957.

The New York Hospital-Cornell Medical Center sponsors conferences for those in practice. The conferences are reproduced in these books. Volume 5 reports discussions on sinusitis, peptic ulcer, mitral stenosis, carcinoma of the cervix, essential hypertension, carcinoma of the breast, cerebrovascular accidents, abnormal coagulation and thrombosis, sterility and impotence, amebiasis, fluid and electrolyte balance, pitfalls in laboratory diagnosis, amenorrhea, and dysmenorrhea; Volume 6 contains talks on whether patients should be told the truth about serious illness; trichinosis; cancer of the thyroid, the prostate, and the esophagus; lung tumors; portal hypertension; bone tumors; the early detection of heart disease; various skin infections, poison ivy, and contact dermatitis; encephalitis and Parkinsonism; endometriosis; consultations with anesthesiologists; and gout. Three to six experts, mainly from New York City, talk on each subject. The editor summarizes each chapter.

Medical conferences are of two kinds. The first is the discussion of a subject which cuts across the conventional barriers of medical education. Those in practice miss such talks, whether held with friends at the lunch table or given formally at a teaching center. This particular series includes a few such topics: "Pitfalls in Laboratory Diagnosis" and a stimulating discussion, "Should Patients Be Told the Truth About Serious Illness?" by a priest, a lawyer, an internist, and a psychiatrist; both of these are worth printing. The second type of medical conference is the formal presentation of a conventional subject, such as peptic ulcer or heart failure. In this case a polished product needs careful planning, slick case presentations, practiced speakers, and a firm moderator. Wit helps. It should cause no surprise that the New York Conferences, like those elsewhere, are sometimes good, sometimes desperately unsatisfactory; what is surprising is that the discussions have not been pruned by fierce cutting or by omission, both of which would raise these books from mediocrity to excellence. The discussion on the early detection of heart disease, for example, is like percussing the liver—dull, inaccurate, and often redundant. The conference on sinusitis meanders over twenty-four pages and is well summarized by the editor in three. Indeed, the only disadvantage of the praiseworthy factual summaries by Forkner is that they emphasize the wooliness of the spoken word.

Richard Steele wrote in the *Tatler*, in the eighteenth century, "Reading is to the mind what exercise is to the body." This is as false and as true as most similes, for all mental exercise is not reading, nor is all reading mental exercise. In Steele's day physicians needed to read more. Today we should read more selectively. For reading may be as good a way of avoiding thought as are television, poker, or gin. Those in practice look for books to help maintain their academic standards. Do not buy the books under review unless you can read very selectively. Better to buy a new edition of a standard textbook. Read these volumes if you are in medical isolation—to show how little this matters.

DANIEL B. STONE, M.D.

Shock and Circulatory Homeostasis. By Harold D. Green, M.D., D.Sc. Price, $4.75. Pp. 337, with 53 tables and 78 figures. Josiah Macy Jr., Foundation, 16 W. 46th St., New York 36, 1957.

The transactions of the fifth and final conference on shock and circulatory homeostasis, sponsored by the Josiah Macy Jr., Foundation, brings to the reader the deliberations of a

distinguished group of investigators from a variety of professional disciplines, all of them having strong interest in this field, reflected in their substantial contributions to it. Each of the topics, which include the role of hepatic blood flow, bacterial factor, protection afforded by Aureomycin, blocking agents, humoral factors, hypothermia and chlorpromazine, and the lymphatic system as related to experimental shock, is introduced by the presentation of the methods and results of the researches by one of the participants. Experiments conducted in the germ-free rats and the hepatic ferritin systems are also discussed. The presentations served as a departure point for the recorded informal discussion by the participants. Each of the nine sections includes a current and useful bibliography, tables, and diagrams of experimental data. The table of contents and the index add to the usefulness of this book. The type is large and readable; the binding, satisfactory. This monograph will be invaluable to the researcher in this field and of considerable interest to those concerned with related clinical problems.

JOSEPH A. BUCKWALTER, M.D.

Research in Nursing. By Amy Frances Brown, R.N., B.Ed., M.S. in N., Ph.D. Price, $5.75. Pp. 352, with 31 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1958.

During the past decade the spotlight has been focused on the need for more and more research in nursing. Until the last five years research in nursing has for the most part been carried out by non-nurses, primarily the sociologist and psychologist. Professional nurses are aware that if nursing is to advance with other professional groups a corps of nurse-researchers must be prepared to do their own research; to assist other disciplines in studying nursing; and, most important, to interpret the findings and draw implications for nursing from the research reported.

The question is often raised by those who study nursing, "Is there any extensive, comprehensive body of knowledge in nursing beyond the master's level?" Basic research in nursing can help to find the answer to this question. Research in this area is essential if nursing is to meet all of the attributes of a profession.

The nurse-researcher, the teacher of research methodologies, and the student-researcher will each find haven in "Research in Nursing."

The author states, "Research is essentially a search for truth." This is in essence the theme of "Research in Nursing," for within the chapters of this book the reader will find the description of the tools to do research. Research—what it is and what it is not—is clarified. The author's discussion further helps to clarify the ambiguities about the variety of studies carried out in nursing.

The agencies carrying out nursing research, a description of the American Nurses' Association clearing house for studies, research publications in nursing, and information about grants and fellowships are included in the book. A selected number of a variety of research projects now being conducted in nursing are described, providing a succinct summary of the many areas in nursing that are researchable.

Three chapters are devoted to the steps in the research process. Under each section selected references are provided for the reader seeking more detail. For example, the chapter, "The Collection, Analysis, and Interpretation of Data," describes a variety of ways in which data can be analyzed. Examples are provided, giving a step-by-step approach to each method. Those wishing more detailed derivations and other applications will find the selected references most helpful. Particularly valuable is the inclusion of information on the usefulness and limitations of each approach.

The graphical presentation of data is often neglected or used incorrectly in many research reports. Illustrations are provided, describing how graphic materials can be used correctly to present findings in a meaningful way.

Several chapters have been directed to methods and techniques of research, describing how the historical, descriptive, and experimental methods can be used to do research in nursing. Examples from nursing studies are given to illustrate each method.

Two detailed studies are included, which provide helpful clues in seeing how the various steps in scientific design can be carried out. The reader will probably wish for more illustrations in nursing, but the novice in nursing research will soon learn that the best way to learn about research is for the researcher to carry a study design to its completion.

Those seeking possible areas for study in nursing will find the chapter, "Studies Needed in Nursing," filled with a wealth of suggestions.

The reader seeking a comprehensive review of nursing research today and the tools needed to do this research will find Dr. Brown's coverage of the field to be extensive, with helpful sources provided throughout the book for the researcher wishing more detail.

FAYE G. ABDELLAH, R.N., ED.D.

Electrocardiography. By Michael Bernreiter, M.D. Price, $5. Pp. 134, with 91 illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1958.

This is an inadequate and frequently misleading treatment of a complex subject. The novice will be led astray, and the moderately advanced student could only be interested in pointing to its deficiencies. In view of the many excellent texts available, the less said about this one the better.

HANS H. HECHT, M.D.

Intracardiac Phenomena in Right and Left Heart Catheterization. By Aldo A. Luisada, M.D., and Chi Kong Liu, M.D. Price, $9.50. Pp. 179, with 98 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1958.

Much of this monograph is devoted to the analysis and interpretation of cardiac pressures and pulses, normal and abnormal. Some of this information was published in Dr. Luisada's earlier text, but this volume also incorporates information on intracardiac phonocardiography and intracardiac electrocardiography. The text is a fairly comprehensive survey of these phenomena and will be valuable in supplying broad general knowledge in these areas. The authors have not attempted to make this a detailed manual on cardiac catheterization techniques or on the interpretation of data. Relatively little information is given on the characteristics of monometers and recording systems or on the theoretical aspects of dynamic pressure recording. One chapter is devoted to the problems associated with the production of artifacts. An understanding of such problems is important, considering the difficulties in making valid pressure recordings in human subjects with the techniques and instruments now available. An appreciation of these pitfalls will help to avoid misinterpretation and "over-reading" of records. The book is illustrated adequately with large clear reproductions of actual recordings. Although this text is probably of limited interest to the clinician, it will be useful to the clinical investigator and the clinical physiologist in the cardiovascular field.

E. O. THEILEN, M.D.

The Johns Hopkins Hospital and The Johns Hopkins University School of Medicine. By Alan M. Chesney, M.D. Price, $6. Pp. 499, with many illustrations. The Johns Hopkins Press, Homewood, Baltimore 18, 1958.

The second volume of this chronicle of "The Hopkins" carries us from the years 1893 through 1905, from the year of entry of the first medical class through the next eight years. This book is not simply a chronicle in the limited sense of being of interest only to those who have had close personal association with The Johns Hopkins Hospital, Medical School, or University. It provides us with the raw material upon which decisions were made and a fresh curriculum for a new medical school was established, and many of the complex interrelationships between a hospital and medical school were established in the university setting. Here medical people could pursue their investigations and do their teaching as a band of scholars, rather than merely a guild of artisans or the journeyman tinkers so many proprietary schools of the day had. This was the first American private medical school under university auspices in which the mutual support and help, which a hospital gives to a medical school and a medical school to a hospital, came to fruition, with pleasant personal associations among highly trained men of good will who felt the sense of mission. Their contribution has altered the course of medical history in this country from that time forward.

Despite the long opposition to the study of medicine by women, fomented by the Victorian notion that anatomical knowledge and medical facts were incompatible with proper lady-like manners and virtue, the final acceptance of women in medicine was ordained at the opening of The Johns Hopkins Medical School, since some of the endowment was available only if women were admitted on the same terms as men. Of the distinguished women in American medicine, a fair number had their training at Johns Hopkins. A commentary, which requires nothing but the stating, is that it was only the pressures of World War II that finally enabled women to join their brothers as aspiring physicians in the celibate cloisters of a hitherto masculine Harvard Medical School.

To people who are interested in the problems of a curriculum, the perennial academic Ping-Pong ball, it is refreshing to see how, year by year during the first four years of The Johns Hopkins Medical School, the curriculum emerged like a butterfly splitting its cocoon rather than as one developed from intensive committee work.

The classes at first had no limit on the number admitted. The fear then was that the very high standards for admission would keep the number down, perhaps even frighten everyone away. But the word of the exciting new school in Baltimore got around, tempting the scholar and keeping out the trifler. Those interested in the history of internships will note that the interns rotated through the few services which existed. Straight service internships came later.

The rise of specialization and the continuing proliferation of new departments and the shifting hegemonies of departmental control, such as whether gynecology belonged in surgery or in obstetrics, are illustrated in an interesting fashion. Likewise, the slow growth of routine laboratory work from procedures possible only in research laboratories is shown as it emerged with the development of the hospital and medical school.

Perhaps best of all, one sees arrayed men of heroic proportions. A few pioneers were able to achieve the very high goals set for them by their wise directors and sponsors and by themselves. Johns Hopkins, a rich merchant and tycoon, ploughed back into socially creative works money he had earned in the market place. Gilman, Billings, Welch, and Remsen had the wisdom to select fine leaders, men who would have been outstanding anywhere. Osler, Halsted, and Kelly, clinicians, investigators, and extraordinarily proficient technicians, seemed to have been guided to a great extent by Mall, whose organizing and directing hand is seen in many of Welch's accomplishments. Although the multifarious jobs of Welch ultimately led him to become "the tomb of manuscripts" in his overwhelming editorial duties, his wisdom, honesty, and skill left traces which were to be seen in the accolade given The Johns Hopkins Medical School in the Flexner report, "Medical Education in the United States," in 1910.

For those with personal or traditional connections with "The Hopkins," the pictures, class rosters, and schedules of the lusty, growing school provide real treasures. Thus, with Volume II, Chesney has carried the story of the great plan and purpose of a medical school as a university within a university to its fulfillment. American medicine had passed through its novitiate with the successful establishment of The Johns Hopkins Medical School. If in later years the towering stature of the school seems to be reduced it is because others have risen in emulation. The next volume is awaited with eager anticipation.

WILLIAM B. BEAN, M.D.

Mental Health in College and University. By Dana L. Farnsworth, M.D. Price, $5. Pp. 225, with no illustrations. Harvard University Press, Cambridge 38, Mass., 1957.

Student populations in some 1,500 United States colleges and universities now range in the neighborhood of three million, a figure that, if all goes well, is expected to double in the next two decades. Unmindful of the discouraging statistics on Selective Service rejection rates and following our ancient tradition to equate youth with strength, we tend to think that, for the most part, all of these young people are robust and free from significant defects and illness. Such customary illusions are quickly dispelled from the minds of administrators and physicians charged with the responsibility of providing medical care for college students. Where comprehensive health services have been made available, the daily record of clinic visits is astonishingly high and the number and variety of diseases and injuries encountered suggest over-all morbidity rates comparable to those reported for other age groups. Many of these illnesses stem from increased exposure and susceptibility to infectious diseases. Another sizable contingent is injuries related to athletic activities and to quixotic bumptiousness in tilting with the physical environment. Again, as in general adult medical practice, a disconcertingly large segment of symptoms and disabilities represent psychologic and somatic responses to stress, for many psychosomatic patterns begin early in life.

College students are ostensibly fortunate young men and women who have not only been granted a halcyon reprieve before commencing the difficult business of living but at the same time afforded ample leisure and expert instruction for preparation and progress toward a goal in life. Moreover, this grand experiment usually takes place in a Laputan island of architectural and philosophic splendor, floating its ephebic subjects above the mundane strictures of parental and parochial authority, exciting them with novel opportunities for the development

and expression of independence in thought and action, and exposing them to tolerant pressures for mental growth, book learning, social education, and the pursuit of illusions and other bents natural to their age. If it comes as a discomforting surprise that among this group of young people, carefully selected by aptitude and past performance for advancement in knowledge and leadership, so many should incur delibitating stress symptoms, we must reflect that the college experiment, ideal and opportune as it is, occurs at a time when personality development and adjustments are at best shaky and unpredictable. College undergraduates are really on their own for the first time, desperately engaged in finding themselves as individuals, and obviously less secure and contained than they were a few years earlier. A few years later, at the graduate level, other factors—motivational, domestic, financial, and military—frequently arise to interfere with the educational plan and effort. College turns out, in fact, to be a tough proving ground, where many fail outright and far more limp along with one foot on and one foot off the path. For those who try the course, there are tremendous personal, parental, and social pressures to compete and to finish. In spite of Mark Twain's admonition not to let schooling interfere with education, failure to make the grade leads often to humiliation, guilt, discouragement, and loss of direction and success in life.

College faculties, administrators, and physicians will find in Dr. Dana Farnsworth's book a wealth of information and philosophy about human interrelationships at the student level. A relatively short, readable monograph, styled in easy lay conversational prose, it sets the pitch for a responsible over-all attitude toward mental health in institutions of higher learning. These pages represent a condensation of the author's own extensive experiences and researches in student health, and his discussions, straightforward and authoritative, are amplified and reinforced by illuminating quotations from other educational leaders who have at one time or another focused their perspective upon various aspects of college life. Comprehensive in scope and detail, successive chapters discuss "The Need for Mental Health"; "Emotional Maturation"; "Student Customs, Morale, and Attitudes"; "Emotional Stress"; "Counseling and Psychotherapy"; "The Administration and the Psychiatrist"; "Development of College Mental Health Programs," and "Emotions and the Curriculum"—this last, a common-sense and constructive plea that colleges give some thought to teaching students to learn something about themselves. A strong hope is entertained throughout for the development and furtherance of mental health programs that in addition to providing medical service for emotionally handicapped and mentally sick students would also seek to detect and alter bad conditions, policies, and regulations in the college itself and thus accept some measure of responsibility for the maintenance of an environment more favorable to learning and success in the over-all educational venture.

Encouragement in the growth of hygienic cusocial attitudes is of course the traditional goal of the entire university community, for all colleges themselves constitute grand-scale mental health programs. How to provide attention to the developmental needs of the individual student has long been a concern of the conscientious teacher. As suggested by Cardinal Newman some years before technology, the essential *idea of a university* is "an alma mater, knowing her children one by one, not a foundry, or a mint, or a treadmill." Since foster mother is fast becoming like the old woman who lived in a shoe, she cannot really know about all of her children. Aside from their broader attributes and policies that influence student morale, many colleges and universities have so far been limited to an attempt to provide individual mental health services to those students who directly seek help or whose physical symptoms or aberrant behavior indicate that they are in trouble of some sort. The inherent difficulties in reaching and holding these people and obtaining significant aid for them are not insurmountable but very formidable indeed.

Among the readers of this volume there may arise some variety of opinion as to the most practical means of achieving the purposes of a mental health program and some question as to the possible disadvantages to be incurred in emphasizing mental health as if it should be considered to some extent medically apart from physical health. Possibly because of its history and the major professional interests of its proponents, mental health movements connote mental ill health to many people, and the much deplored scarcity and unpopularity of organized mental health programs reflects an ancient recidivistic antipathy toward the whole subject. (For a chagrined description and evaluation of these disconsolate antipsychiatric prejudices, attention is invited to the report "Closed Ranks," somewhat sportingly advertised on the jacket of Dr. Farnsworth's book.) Many men in the street adopt the attitude or defense that for many reasons it is better to "let your mind alone," and society, although

more tolerant than formerly in that it accepts explanation for mental sickness to some extent as an excuse for it, still appears somewhat unfavorable in its attitudes toward its members who have trouble in ordering their lives. Or at least those members think so. By far the majority of college students with adjustment problems develop psychosomatic symptoms and report to a general practice type clinic for physical relief. It is in the broad diagnosis and treatment of the presented clinical symptoms that an opportunity knocks for the conscientious physician artfully to explore related mental and situational stress factors and to influence and direct the patient toward further resources for additional guidance and specialized treatment.

It is only in recent years that these resources, implicit in the concept of a mental health program for colleges, have been visualized and to some extent organized. At Harvard, elaborating upon the broad foundation established by A. V. Bock, Dr. Farnsworth has instituted a model cooperative system, based upon the participation of student counselors, faculty, administrative officers, college physicians, and psychiatrists. Similar developments at other schools, practical as well as idealistic, stress the salvage of the individual student's educational program and the conservation of the student population. These humane and orthodox professional orientations are concerned primarily with health education for preventive medicine, with the prodromes of trouble—physical and nervous symptoms, potential-performance discrepancies in grades, classroom absenteeism, rebellious social conduct, and other behavior aberrant to the alleged college purpose—and with the use of modern medical techniques to find out what has gone wrong and to help the student reestablish himself. It is tacitly assumed that when young people leave their families and enter college further growth and security are fostered by a strong identification with Alma Mater and that over-all health adjustments are to a large extent a joint responsibility of the student and the academic community. Where comprehensive medical facilities are available, colleges may find a strong social and professional obligation not to pass any health problem back to parents and home communities, often handicapped by inappropriate or inadequate resources for supplying what is needed by the student at the time. For institutions able and willing to accept this challenge, Dr. Farnsworth's book provides basic concepts and principles of lasting value. It should be in the hands and heads and hearts of all of the people engaged in college work.

ANDREW D. HART, M.D.

Ward 4. By James Howard Means, M.D. Price, $4.50. Pp. 187, with 5 illustrations. Harvard University Press, Cambridge 38, Mass., 1958.

The face of clinical medicine has undergone a profound revolution within the lifetime of all practicing physicians. This revolution has been witnessed in detail by many people still living. Indeed, some have had an active part in giving direction and form to the revolution. The rise of laboratory medicine, the development of metabolism wards, and the building of whole hospitals devoted not to the care and cure of the sick but to an analysis of mechanisms and processes, characterize our time. No one has written a history of the changes as they have occurred. Such information as is available for the most part exists as a documentary or chronicle rather than an analytical history. "Ward 4" does not tell us the history of the rise of clinical research. It does give the narrative of one particular metabolic unit and the people whose activities had this for a home base and whose interests determined the course research was to take. The book is a chronicle then and not a history. Its method is anecdotal. At times its approach oscillates between provincial and parochial. Ward 4 is not presented as a unique or isolated phenomenon but is an outstanding example of metabolic units. Under the auspices of Ward 4, originally supported through the largess of individual benefactors, a unit small in scope but large in purpose developed, where ideas directed research. Projects did not direct investigators. In addition to the author, interested in thyroid disease, a distinguished line of investigators included Aub, Bauer, and Albright and their numerous colleagues and disciples, all of whom have made history in clinical research in this country. The careers and the productivity of the persons who have worked on Ward 4 need no embellishment for those who are familiar with American medicine.

For someone not aware of clinical research as it has arisen in America and throughout the world, this book might leave a number of misconceptions. The implication that the last word in lead poisoning was written in 1926 omits the radical revision of ideas and practical solution of some of the industrial problems by Kehoe at the Kettering Laboratory in Cincinnati. One might surmise that liver biopsy had been invented and first tried in Ward 4. Sheehan's contributions to understanding pituitary dysfunction are not mentioned. These

omissions, permissible in a chronicle, detract from a broader scope for a book of this type, which might have led to generalization and pointed some lessons.

WILLIAM B. BEAN, M.D.

Men, Molds, and History. By Felix Marti-Ibañez, M.D. Price, $3. Pp. 114, with no illustrations. MD Publications Inc., 30 E. 60th St., New York 22, 1958.

Felix Marti-Ibañez has had a number of successful careers. He has been teacher, administrator, medical historian, psychiatrist, medical director of pharmaceutical concerns, and editor. In the process he has done much writing and now is launched as an author. Perhaps because of his hot-blooded Spanish background, he has a style poised somewhere between baroque and rococo, which at times produces in the reader manifestations of hyperpyrexic vertigo and intellectual heat exhaustion, analogous to the experience of an unacclimatized person who suddenly finds himself walking in a humid jungle. Praise which is usually reserved for the dead seems too fulsome in his dedication of the book. The unguarded indulgence in a ripe verbal felicity often splashes over into the intoxicating verbosity of linguistic compost. Fortunately acclimatization takes place, and the overworked olfactory sense fatigues easily. This book is full of much interest for the medical historian.

The story of antibiotics is told in a series of separate essays, strung together loosely on a common theme. A very extensive knowledge of medical history, classical background, and an interest in words and expressions carry the reader along a journey through one of the exciting new byways of history. The essay on translation is excellent. The praise of Fleming and the oft-told story of penicillin is modest and delightful. So, after one has become accustomed to the ornate style, he finds much of interest and charm in "Men, Molds, and History."

WILLIAM B. BEAN, M.D.

The Psychiatrist and the Dying Patient. By K. R. Eissler, M.D. Price, $5. Pp. 338, with 3 illustrations. International Universities Press, Inc., 227 W. 13th St., New York 11, 1955.

American physicians on the contemporary scene suffer in aggravated form from their rejection of the very idea of death. Rarely are they able to face death in a patient with equanimity. The vigilant and sympathetic support which patients rightly expect of their physicians may be lacking. This book, written by a perceptive and thoughtful psychoanalyst, is one of the rare contemporary considerations of the problem of death and dying which really even tries to throw light on the subject.

A striking reproduction of the death mask of Beethoven serves as frontispiece and sets the tone for this scholarly and searching essay. Death as a precondition for life and the impossibility of physical immortality with infinitely protracted longevity are taken as basic assumptions. The contributions of Heidegger, Simmel, Ehrenberg, and Freud, as well as a review of a great deal of miscellaneous and out-of-the-way material published mostly in this century, define the topic and fill out the theme. In most instances what Eissler says about psychiatrists could apply to any physician who is helping his patient face the problem of dying. Of all problems, this is the one which our culture and education prepare us for least. The book is a series of essays and case reports, which may be read individually or as they appear. The chapters are self-contained essays dealing with different aspects of a common theme. They are not arranged in a strictly logical order. The book is a thanatology rather than a thanatopsis. It is no small tribute to the skill of the author that he has done a work both scholarly and moving. The summing up takes the form of a discussion of *orthothanasia*, which is defined as the right, true, and proper manner of dying. Orthothanasia versus euthanasia, the modern concept of time, the relation of death to the biological sciences, and a searching commentary on the psychoanalytic constructs about death are discussed in a challenging way. This book provides much useful historical material dealing with the direct approach to individual death as the physician faces it. What Eissler says is applicable to any physician who admits his concern with the problems of death in an individual patient and his family. Only in rare spots does the meaning tend to fray out at the edges in the not always clearly defined nomenclature of Eissler's specialty. Physicians who do not reject the idea and run away from the problem of death might gain much help from this thought-provoking and excellently written study, which is practical as well as speculative.

WILLIAM B. BEAN, M.D.

Epilepsy. By Manfred Sakel, M.D. Price, $5. Pp. 204, with no illustrations. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1958.

This book is a rather disconnected arrangement of facts and speculations about epilepsy. Part II, "Theory and Proposed Method of Curing Epilepsy," occupies eighty-five pages and represents the aftermath of Sakel's demonstration, some twenty-five years ago, that induced hypoglycemia would often profoundly improve the mental state of the schizophrenic. Physiologists as well as patients have benefited from the studies that Sakel's work inspired. His speculations with respect to epilepsy now appear as reiterated ideas, such as the following ones:

"Since the early insulin convulsion resembles the idiopathic epileptic convulsion in its clinical details, it is suggested that their mechanisms may be the same and that their purposes are identical. Both act to preserve the hormonal, chemical and biological integrity of the individual by stimulation of the sympathetic nervous system. . . . The type of convulsion is the outcome of the fight for supremacy between the vagus, externally overstimulated by insulin, and the sympatheticus, overcompensated by the internal provocation of the adrenocortex. . . . In the case of a convulsion there is a sudden stimulation or irritation of the vagal end. The convulsion results because the opposite end of the system, the sympatheticus, and with it the adreno-cortical system overshoots its goal in its effort to hold its own. . . . The convulsion is the expression of the fact that the sympatheticus has succeeded in re-establishing the balance. . . . My acceptance of idiopathic epilepsy as a self defense mechanism working through the vegetative nervous system to establish the neuro-hormonal equilibrium was based on the interpretations of the physical manifestations of the epileptic symptomatology."

To correct this imbalance, Sakel "implanted" slices of the thyroid gland of a man with a metabolic rate of +60 into the thyroid gland of two epileptic patients. After the operation he learned that the donor was an epileptic whose remissions from seizures coincided with periods of exacerbation of his hyperthyroidism. The two recipients of the thyroid graft were institutional epileptics whose future had been written off as hopeless. One of these made a startling recovery with respect to seizures, mentality, and work record. The condition of the other was unchanged. The author assumes that the graft "took" in the first case and did not "take" in the second. The metabolic rate of the recipients was not determined either before or after the operation. Sakel concludes this section, "Knowledge that has been accumulated thus far has already helped to develop an etiological treatment for idiopathic epilepsy and other disorders of the emotions and the mind."

The first hundred pages of the book are occupied by routine statements of the symptoms and causes, the electroencephalogram, and the therapy of epilepsy. The book ends with a seventeen-page recital of eight cases of grand mal or psychomotor epilepsy, whose histories seem irrevelant to the author's theory. There is no reference list of the few authors mentioned and no index.

Sakel's argument would carry more weight if certain questions were dealt with. Many students of epilepsy believe that the divergent vagal and sympathetic symptoms that accompany a grand mal are passive rather than active expressions of the fit. They would stress the importance of seizures that are without convulsions or loss of consciousness and are variously termed autonomic, visceral, vegetative, or diencephalic epilepsy. They would wonder if prescription of desiccated thyroid would have served the author's purpose better than the attempted transplantation of gland tissue.

Unfortunately, Manfred Sakel died before the manuscript was completed. Five psychiatrists helped to annotate and bring the material up to date. The volume is published "as a fitting memorial to the life work of a noble pioneer." As a memorial, the book will please the many former companions and friends of Manfred Sakel. Other readers would have appreciated some account of his life. His photograph is on the jacket. The binding is gray cloth with an attractive blue and gold label.

Hypoglycemia and epileptic convulsions may at times impinge, but never the twain shall merge.

WILLIAM G. LENNOX, M.D.

Third Tissue Homotransplantation Conference. By Otto V. St. Whitelock. Price, $4.50. Pp. 329, with 94 illustrations. Annals of New York Academy of Sciences, 2 E. 63d St., New York 21, 1958.

Away from the well-trodden paths of clinical medicine and remote even from the established fields of investigation, such as cardiac disease, arteriosclerosis, cancer, or infectious diseases, labors a force of workers silently intent upon a single goal. Though few of them will mention it, still their ultimate goal is apparent to all—the successful transplantation of tissue from man to man. What a pity that man must "wear out" in a single place, be it heart, lung, liver, or kidney, while the rest of him remains whole and useful. The dreams of "spare parts" transplantation have been legion, yet the obstacles have been seemingly insurmountable.

I pondered these thoughts as I read the "Third Tissue Homotransplantation Conference" articles, admiring the ingenuity of some and industry of others who contributed, each in his small way, to a greater understanding of the mysteries of tissue transplantation. The parade is endless, varied, ingenuous or common, brilliant or blunt, but always directed toward the same objective. Time and again the "uniqueness of the individual" was confirmed and reconfirmed, until one might doubt that "commonness" shall ever be attained. Yet there are successes—faulty, incomplete, and temporary though they may be—and hope grows again to anticipation, even to conviction, that the goal will be achieved. Whether it will come abruptly, as a result of some brilliant investigation, or, more likely, gradually and in small increments, the reader can scarcely doubt that come it will.

This single achievement would stagger the imagination in its implications. The role of the surgeon would become paramount as he replaced worn or diseased organs. Life expectancy would leap ahead, creating added social and economic problems but augmenting the security and productivity of man in his "years of wisdom." Even malignant disease could be treated more effectively if entire organs could be removed and replaced.

To the student of nature, the investigator, or the curious in any field of biologic endeavor, this volume will mark a milestone in his efforts to interpret and to apply the lessons of nature. It is well done.

ROBERT E. HODGES, M.D.

A Way of Life and Other Selected Writings of Sir William Osler. Edited by G. L. Keynes, M.D., F.R.C.S. Price, $1.50. Pp. 278, with 5 illustrations. Dover Publications, Inc., 920 Broadway, New York 10, 1958.

The publication of a paper-bound edition of this delightful collection of William Osler's essays puts it within the reach, and I hope in the hands, of all medical students who do not already own a copy. There is no effort to expunge, rearrange, or otherwise alter the papers as Osler wrote them. This book was first put out by the Oxford University Press, under the aegis of the Osler Club, in England. It includes a charming introduction by Keynes and has an index which is chiefly an index of personal names, but even this is of some help. Six of the sixteen essays are biographical, and many of the others are full of allusions to famous historical people—doctors, humanists, scholars—and cranks. Each of these essays is worth the time of reading and rereading, and even the poorest student should be able to afford the modest price. Here then is a rare opportunity for students of medicine from cradle to grave to obtain firsthand inspiration from the man who undoubtedly was the most illustrious person the western hemisphere has contributed to the world of medicine.

WILLIAM B. BEAN, M.D.

Atrial Arrhythmias, Digitalis, and Potassium. By Bernard Lown and H. D. Levine. Price, $6.50. Pp. 222, with 53 illustrations and 14 tables. Landsberger Medical Books Inc., New York, 1958.

In this monograph, the authors take up in detail the disorders of atrial rhythm which may be induced by digitalis and characterize the particularizing disorder as paroxysmal auricular tachycardia (P. A. T.) with block. The delineation between P. A. T. with block and auricular flutter or paroxysmal auricular tachycardia is difficult, and great emphasis is placed on differentiating this hybrid disorder from conventional forms. The literature of the past half century has relegated P. A. T. with block to an area of dubious clinical significance and questionable origin. The authors present evidence, on the basis of the analyses of some one hundred fifty episodes of P. A. T. with block, that the disorder is rather common, having a distinct ECG

pattern, and that in a majority of instances the etiology is related to digitalis therapy. The interplay between digitalis and body potassium is involved in this atrial arrhythmia much in the same manner as in ventricular arrhythmias but may include, in addition, a vagal component.

The case history analyses are amply illustrated with fifty-three ECG tracings, and, at the end of the book, a theoretical discussion of the possible mechanism is undertaken qualitatively in terms of conventional physiological theory.

The book is written primarily from a clinical standpoint, but it is also stimulating from a theoretical point of view and is a fitting sequel to the authors' original publication, "Current Concepts in Digitalis Therapy."

ALEXANDER C. KEYL

The Practice of Infectious Diseases. By Louis Weinstein, Ph.D. M.D. Price, $8.50. Pp. 501, with 4 tables. Landsberger Medical Books, Inc., New York, 1958.

To begin, this is an excellent book. If you want to know of the tremendous developments in the diagnosis and treatment of infectious diseases since you obtained your M.D., this is the book for you. You will be astonished at how much factual knowledge has accumulated since you learned fevers, in your medical childhood. Here is the combined approach of the physician and the bacteriologist, which is so greatly needed.

No one would dream of treating a patient with coronary artery occlusion without confirming the clinical diagnosis with an electrocardiogram. All too many physicians, however, are treating fevers without knowing first, whether an infection is present; second, what it is, and third, what antibiotic to use. Throughout the book there is recurrent emphasis on careful clinical assessment, Gram-stained preparations, diagnosis by culture, sensitivity tests where required, and a careful follow-up. The approach is systematic, namely, infections of the upper and lower respiratory tracts, of the skin, of the nervous system, etc.

Do you know the best time to take a blood culture, the bacteriological statistics of S. B. E., the usefulness of the C-reactive protein test, at what point fever becomes dangerous, what diseases to treat with sulfonamides, the modern treatment of syphilis, or how to run down a false-positive serological test for syphilis? If you do not, the answers are to be found in this book. Chapters 2 and 3, on the principles of treatment and prevention of infection, are a very good outline of chemotherapy.

As this book will undoubtedly be published in subsequent editions, a few points of criticism are in order. The index is very poor. The pagination for some items is wrong. Although mentioned in the text, Pseudomonas, adenovirus, ECHO virus, cortisone, Coxsackie virus, Reiter's syndrome, Dodds-Buddingh disease, Iceland disease, and many others do not appear in the index. "Chitton's synovitis," on page 325, should be "Clutton's joints." It is doubtful if the amputation of a diseased member ever did any good in a generalized disease; therefore, it is doubtful whether there is any place for nephrectomy in renal tuberculosis. Capsular swelling for the identification of the pneumococcus has been useful in the past but, as the antiserum is no longer available commercially, it is probable that the test does not belong in a text such as this. A figure of ninety per cent, as the proportion of S. B. E. cases due to a viridans Streptococcus, is now too high, and a mortality (fatality?) rate of ten to fifteen per cent is too low.

Dr. Weinstein represents the new and growing subspeciality of infectious diseases. Just as the biochemist interprets the phenomena of biology in terms of chemistry, so the infectious disease specialist (internist, pediatrician, or veterinary) interprets the phenomena of infectious disease against a background of bacteriology, virology, and pharmacology. The fever hospital has gone (perhaps unfortunately) because the ancillary help that could be attracted there was so poor in quality. Many things have changed: even infection itself. This latter fact we are learning to our chagrin in the present hospital staphylococcal plague. The field of infectious disease, as is pointed out by Dr. Weinstein, is expanding, not contracting. It is time to acquaint our residents with this rapidly developing and interesting field.

This book is recommended to all without reservation as an up-to-date and accurate picture of the diagnosis and treatment of infectious disease.

IAN MACLEAN SMITH, M.D.

Aubrey's Brief Lives. Edited by Oliver Lawson Dick. Price, $5.95. Pp. 447, with no illustrations. University of Michigan Press, 311 Maynard St., Ann Arbor, Mich., 1957.

"Words, no less than men, have a history of their own, and in reading Aubrey after so great a lapse of time, the sharpness of every phrase and sentence is particularly striking." Thus Oliver Lawson Dick justifies his elegant edition of "Aubrey's Brief Lives." If Aubrey is known by physicians today it is for his perceptive, though perhaps not totally accurate, commentary on William Harvey, which has come in for much notice during the recent tricentenary celebrations of Harvey's death. If one savors words and style and if through them he can get even a glimpse into the mental workings of men of another age, he is well served. Thus he may understand and profit by some of the lessons of history. The late Elizabethan times in England form one of the most remarkable phases in the history of the English-speaking peoples. A small upstart country had begun to develop those magnificent skills and traits by which were erected the British Empire and dominions, which spread the English-speaking peoples around the world.

Almost any quotation gives the flavor of this charming book. Much of what Aubrey says seems a little earthy compared with our slightly more staid and dreary speech. This is the fresh morning in the garden of growing English speech. The dew is still upon it. Fascination with the natural world, exposed to view by the Renaissance, was proper subject for everyone's curiosity. Aubrey had a wonderful flare for description. The ability to pinpoint or epitomize the whole form and figure of a man as well as his personality in a few words was illustrated again and again. Strange new insights may occur. For instance, Bacon's charges against women and children as hostages to fortune are seen as rationalizations explained by one word about Bacon which Aubrey prints in Greek.

Dick has let Aubrey write his own autobiography by a skillfully selected and blended group of excerpts from his writings. Thus we get a magnificent view of the man himself and the times in which he lived. He was a man who received sharp buffets from fortune and had much hard luck. Aubrey spent his life embroiled in law courts which wasted his patrimony. He was a victim of frustration, caught in the tangles of his enthusiastic ineptitudes, enmeshed in the traps of a thousand half-done projects, ready to drop everything for casual discourse with some fellow antiquarian or just sheer gossip. He was truly a disorganization man.

He was so much more the collector than the organizer that his extremely ambitious histories and biographies never got to completion but were hurriedly thrown together and published piecemeal. He says about his work, "This Inquiry, I must confess, is a gropeing in the Dark; but although I have not brought it into a clear light; yet I can affirm that I have brought it from an utter darkness to a thin mist, and have gonne further in this Essay than any one before me." This is certainly a fair statement of what he had to say and what he accomplished. Aubrey summed up his own position most astutely when he wrote in his life of Hobbes, "But one may say of him, as one sayes of Jos. Scaliger, that where he erres, he erres so ingeniosely, that one had rather erre with him then hitt the mark with Clavius." Anyone with any antiquarian tastes or longings will find rich reward and fascinating fare in Aubrey's Lives, especially in the splendid edition which we have available in Oliver Lawson Dick's scholarly work.

WILLIAM B. BEAN, M.D.

The Neurologic Examination. Second edition. By Russell N. DeJong, M.D. Price, $20. Pp. 1078, with 299 illustrations. Paul B. Hoeber, Inc., (Medical book department of Harper & Brothers), 49 E. 33d St., New York 16, 1958.

The second edition of an established textbook and reference on the neurologic examination, this is regarded as an authoritative work which contains a wealth of information for the reader. Important changes have been made in the elaboration of the following subjects: parietal lobes, visual field examinations, ocular movements and nystagmus, extrapyramidal and pyramidal functions, cerebellar functions, electromyography, and spinal fluid examination.

Thus, this edition incorporates the important advances in these phases of the neurologic examination. It can be recommended highly to student, practitioner, and specialist.

A. H. SAKS

Medical Electrical Equipment. Edited by Robert E. Malloy, M.B., F.F.A., R.C.S. Price, $15. Pp. 312, with 238 illustrations. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1958.

So widespread is the use of electrical and electronic equipment in a modern hospital that there are few clinical or research departments which can function effectively during a power failure. The publishers of this work declare their intention to provide "authoritative information on the principles, operation, care and routine maintenance of medical electrical apparatus in terms which do not pre-suppose a deep knowledge of electricity." That such an ambitious undertaking must be judged a failure is disappointing but not surprising.

The book is a collection of essays by twenty-one British workers in the electromedical field. Of these contributors, nineteen are affiliated with commercial companies which manufacture electrical apparatus or instruments. While they have, in the main, made a conscientious effort to avoid "plugging" their own products, only a few of the chapters can make a legitimate claim to generality. Perhaps the main objection to this book is that nearly all the information it contains is or should be provided in manufacturers' instruction and installation manuals.

The book is divided into more than a dozen sections, with little attempt at continuity. This arbitrary division is especially unfortunate in that it reinforces an erroneous but widespread impression that technicians are required to service every small subdepartment. I am emphatically of the opinion that a technician who can maintain an electroencephalograph but who disclaims any knowledge of the principles of electrocardiography or who is unable to repair a spectrophotometer is either lazy or lacks an adequate training in engineering fundamentals. In either case he is an expensive luxury on the maintenance budget.

A further defect, which stems directly from the author's concern with individual pieces of apparatus to the virtual exclusion of first principles, is that most of the equipment described is of British manufacture and suited to the particular needs of that country. There are many differences between American and European engineering practices and terminology, and no attempt has been made—other than the attachment of a dollar price tag—to adapt the work for American users.

In one respect the book deserves commendation; there is a constant emphasis on the risks to patients and staff which electrical apparatus can present if improperly designed, poorly installed, or inadequately maintained.

HAROLD W. SHIPTON

Cold Injury, Ground Type. By Col. Tom F. Whayne, U. S. Army (Ret.), and Michael E. De Bakey, M.D. Price, $6.25. Pp. 529, with 52 tables, 32 charts, and 105 illustrations. Superintendent of Documents, Government Printing Office, Washington 25, D. C., 1958.

This is one of the finest and most comprehensive and detailed books ever written on the subject. The historical review from the Napoleonic Wars through World War II is outstanding in that cold injury has always been a problem for armies in combat during the fall, winter, and spring months. The concise pinpointing of the problem during World War II is noteworthy. The epidemiology, pathogenesis, and pathological aspects discussed are all conclusive. It is important to note that this condition occurs most frequently after a warm-up period following cold, freezing weather and during the periods when the troops are pinned down in trenches, foxholes, and emplacements where proper care of hands, feet, and legs and exercise are impossible. Troops on the move have much less cold injury. The clinical picture, diagnosis, and treatment are covered in a most excellent manner. Col. Whayne is to be complimented on his most excellent handling of the preventive medical approach.

The surgical care, reconditioning, and final disposition of injured patients, by Dr. De Bakey, is in keeping with the skill and excellence he has achieved in vascular surgery.

Since the prevention of cold injury, ground type, is a command function, this volume should be read and studied by all line (command) officers and medical officers of the Regular Army and its various reserve units. It is a must for the library of a physician or surgeon dealing with peripheral vascular disorders. Col. John B. Coates Jr. (MC), Director of the Historical Unit, U. S. Army Medical Service, should be praised for his superior work in producing this volume with its concise, comprehensive illustrations, charts, and photographs.

W. PRICE KILLINGSWORTH, M.D.

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The Biological Effectiveness of Oatmeal Protein

The pattern of essential amino acids in food protein is the criterion of quality by which biological effectiveness is measured. The efficient conversion of ingested protein to tissue protein depends on the concomitant presence of all needed amino acids in proper amounts and proportions at the site of biosynthesis.

Oatmeal exceeds all other whole-grain cereals in the amount of protein it provides. The quality of its protein is good—the distribution pattern of essential amino acids of the protein afforded by the oatmeal-and-milk serving resembles remarkably closely the pattern required by man.

Comparison of Pattern of Essential Amino Acids in Quaker Oats Breakfast Dish* with Pattern of Essential Amino Acids Required by Male Adults

(Values on Basis of Tryptophan as Unity)

	Trypto-phan	Phenyl-alanine	Lysine	Threo-nine	Valine	Methio-nine	Leu-cine	Isoleu-cine
Essential Amino Acids Pattern in Quaker Oats Breakfast Dish* (1)	1.0	3.8	4.2	2.9	4.7	1.4	6.4	4.3
Essential Amino Acids Pattern Required by Male Adults (2)	1.0	4.4	3.2	2.0	3.2	4.4	4.4	2.8

*Prepared from 1 oz. Quaker Oatmeal (dry) and 4 fl. oz. whole milk.

(1) Estimated from values in "Amino Acid Content of Foods", Home Economics Research Report No. 4, U.S. Dept. Agr., 1957, pp. 48, 58. (Quaker Oats protein = 16.7%)

(2) Staff Report: "Rose Reports Human Amino Acid Requirements", Chem. Eng. News 27:1364 (1949).

IN DIETARY MANAGEMENT, virtually regardless of the adjustment to be made, oatmeal proves remarkably valuable. It is low in sodium, low in purines, low in inert residue, high in protein, notable for its vitamin and mineral content, yet not excessive in calories.

Oatmeal is also noted for its significant content of B vitamins and minerals important to physiologic needs. Its delicious taste and easy digestibility further qualify oatmeal as an ideal "habit food" for every day's breakfast.

Quaker Oats and Mother's Oats, the two brands of oatmeal offered by The Quaker Oats Company, are identical. Both brands are available in the Quick (cooks in one minute) and the Old-Fashioned varieties which are of equal nutrient value.

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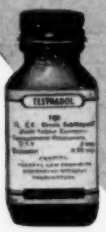

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1. Nussbaum, H. E., Leff, W. A., Mattia, V. D., Jr. and Hillman, E.: Am. J. M. Sc. *234*:150, Aug. 1957. 2. Dunsmore, R. A., Dunsmore, L. D., Bickford, A. F. and Goldman, A.: Am. J. M. Sc. *233*:280, March 1957. 3. Boyd, L. J., Huppert, V. F., Mulinos, M. G. and Hammer, H.: Am. J. Cardiol. *3*:229, Feb. 1959.

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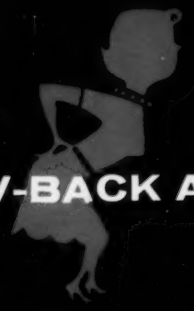

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Jordan and Grossman; Arch. Surg. 74: 871, 1957

Shingleton, et al; Surgery, 42: 12, 1957

Longmire, Jordan and Briggs; Ann. Surg. 144: 681, 1956

Krane; Am. Pract. and Digest, 8: 1275, 1957

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A moderate low-fat well-balanced breakfast for a man of 25 years

When a moderate reduction of dietary fat is indicated, it is worthwhile to consider a basic cereal and milk breakfast which, as shown in the table below, *contributes well-balanced nourishment. This breakfast is moderately low in fat because its fat content of 10.9 gm. provides 20 per cent of the total calories.* It provides "Men, 25 Years" with approximately one-fourth of the recommended dietary allowances[1] of protein, important B vitamins, essential minerals; and provides quick and lasting energy. The Iowa Breakfast Studies demonstrated for young men that a basic cereal and milk breakfast maintained mental and physical efficiency during the late morning hours and that it was superior in doing so when compared either to a larger or smaller morning meal.

recommended dietary allowances and the nutritional contribution of a moderate low-fat breakfast*

Menu: Orange Juice—4 oz.;
Cereal, dry weight—1 oz.;
Whole Milk—4 oz.; Sugar—1 teaspoon;
Toast (white, enriched)—2 slices;
Butter—5 gm. (about 1 teaspoon);
Nonfat Milk—8 oz.

Nutrients	Calories	Protein	Calcium	Iron	Vitamin A	Thiamine	Riboflavin	Niacin equiv.	Ascorbic Acid
Totals supplied by Basic Breakfast**	503	20.9 gm.	0.532 gm.	2.7 mg.	588 I.U.	0.46 mg.	0.80 mg.	7.36 mg.	65.5 mg.
Recommended Dietary[1] Allowances—Men, 25 Years (70 kg.—154 lb.)	3200	70 gm.	0.8 gm.	10 mg.	5000 I.U.	1.6 mg.	1.8 mg.	21 mg.	75 mg.
Percentage Contributed by Basic Breakfast	15.7%	29.8%	66.5%	27.0%	11.8%	28.7%	44.4%	35.0%	87.3%

**Revised 1958. Food and Nutrition Board, National Research Council, Washington, D.C.*

***Cereal Institute, Inc.: Breakfast Source Book. Chicago: Cereal Institute, Inc., 1959.*
Watt, B. K., and Merrill, A. L.: Composition of Foods—Raw, Processed, Prepared. U.S.D.A. Agriculture Handbook No. 8, 1950.

[1]*The allowance levels are intended to cover individual variations among most normal persons as they live in the United States under usual environmental stresses. Calorie allowances apply to individuals usually engaged in moderate physical activity. For office workers or others in sedentary occupations they are excessive. Adjustments must be made for variations in body size, age, physical activity, and environmental temperature.*

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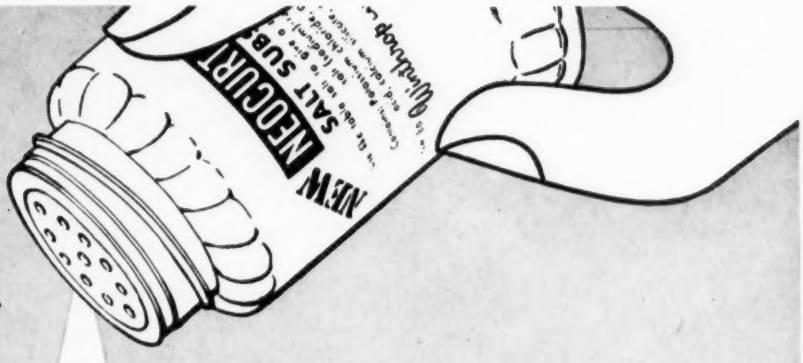

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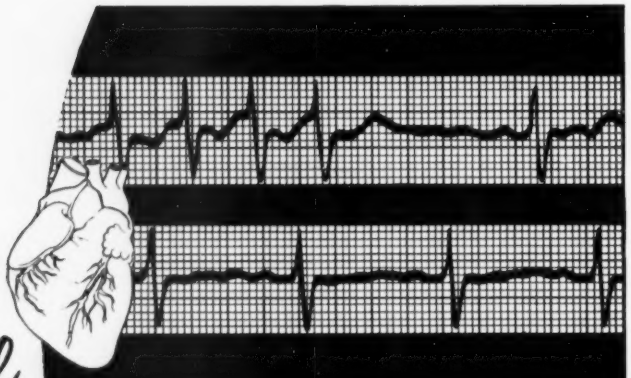

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1. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Archives Internal Med. 100:750, 1957.

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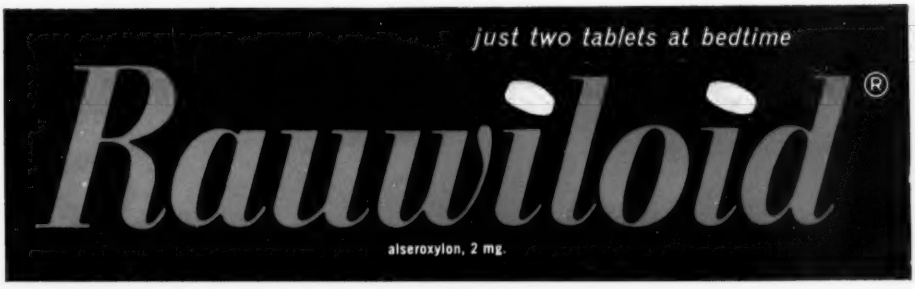

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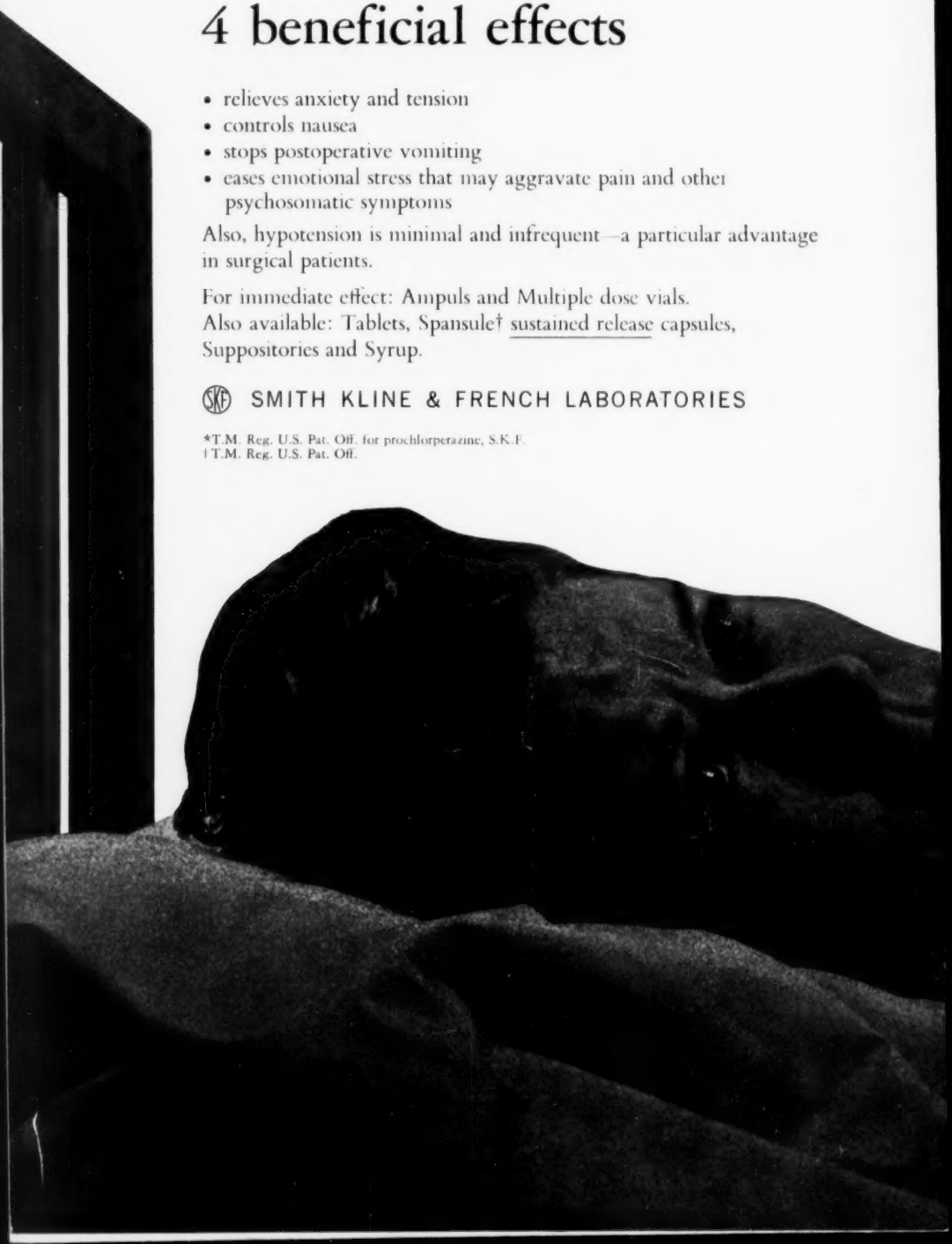
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